Paid Circulation, 33,555

The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 252 MARCH 31, 1955 NUMBER 13

Original Articles

Management of the Pregnant Patient with Cardiac Disease 511
William Horowitz

The Asymptomatic Isolated Pulmonary Nodule 515
Earle W. Wilkins, Jr.

Effects of Anticholinergic Drugs on Pepsin Production and Uropepsinogen Excretion . . 520
Harold M. Silver, Helio Pucci and Thomas P. Almy

Present-Day Treatment of Pituitary Adenomas: Surgery versus X-Ray Therapy . . 524
Gilbert Horrax, Magnus I. Smedal, John G. Trump, Richard C. Granke and K. A. Wright

Medical Progress

Coagulation, Hemorrhage and Thrombosis (Concluded) 526
Benjamin Alexander

Medical Intelligence

Digitalis in Acute Myocardial Infarction . . 536
Norman H. Boyer

By the London Post 537
John Lister

Case Records of the Massachusetts General Hospital . 539

Editorials

Protein Foundation and Research on Blood . . 548
Medical Task Force Report 550
Pathologists Needed 550
Training of Technologists 551

Massachusetts Medical Society 551
Massachusetts Department of Public Health Notices 552
Correspondence 552
Books Received 552
553

New 17th Edition . . . **Fulton's Physiology**

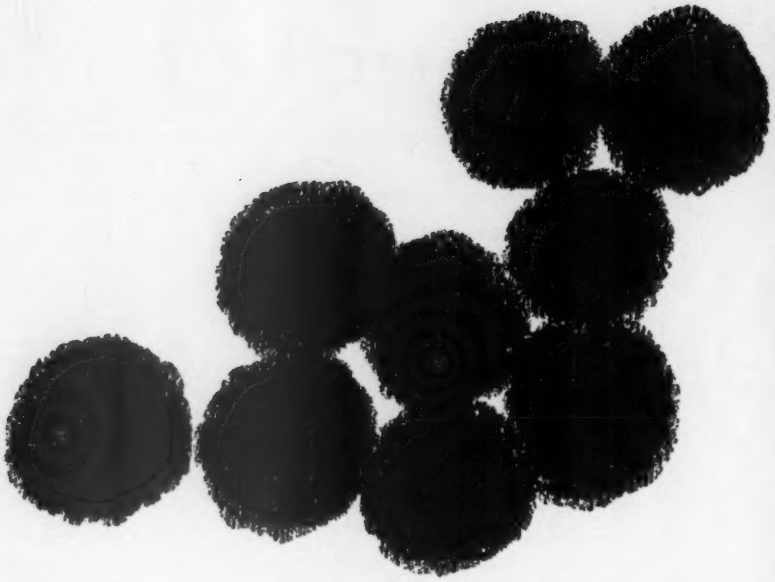
This *New (17th) Edition* represents the most complete and modern physiology text in print today. The presentation is one of orderly simplicity combined with remarkable clarity and force in describing physiologic processes. Clinical aspects are emphasized, especially those which are directly helpful in pathology, diagnosis and treatment.

Maintaining the features which have made it popular for almost half a century, the book has been thoroughly revised and brought completely up to date. The first 7 chapters on Principles of Nervous Activity have been rewritten. The section on body fluids and kidney function reflect recent advances in the field. There are new chapters on Acetylcholine and Energy Transformations in Nerve Cells, and the Hypothalamus.

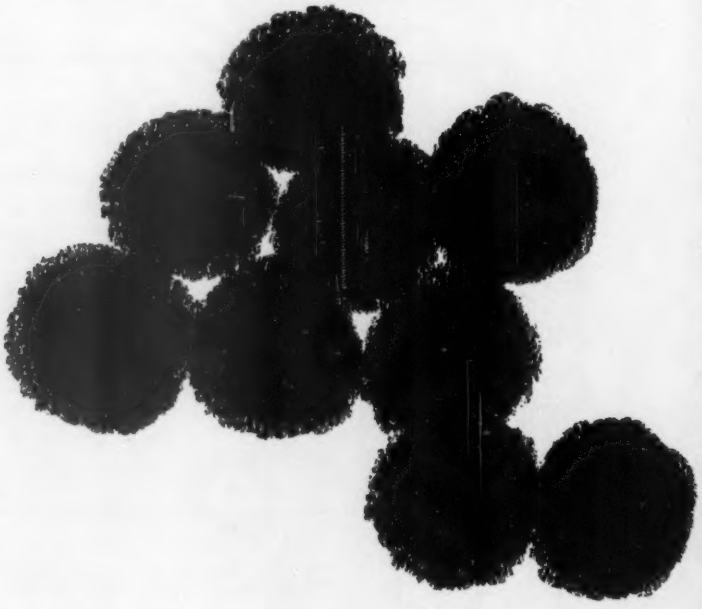
Edited by JOHN F. FULTON, M.D., Sterling Professor of the History of Medicine, Yale University School of Medicine; with the Collaboration of 30 Authorities. 1275 pages, 6¾" x 9¾", with 553 illustrations. $13.50. *New!*

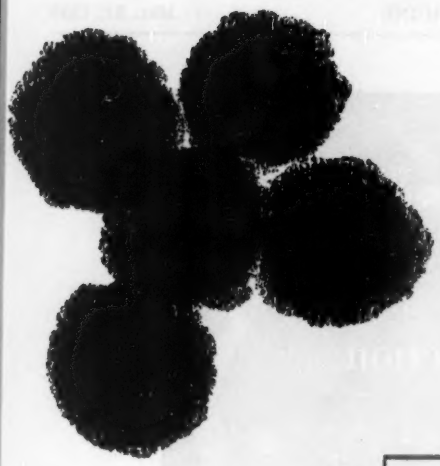
W. B. Saunders COMPANY

WEST WASHINGTON SQUARE, PHILADELPHIA 5



to combat resistant bacteria...





Chloromycetin®

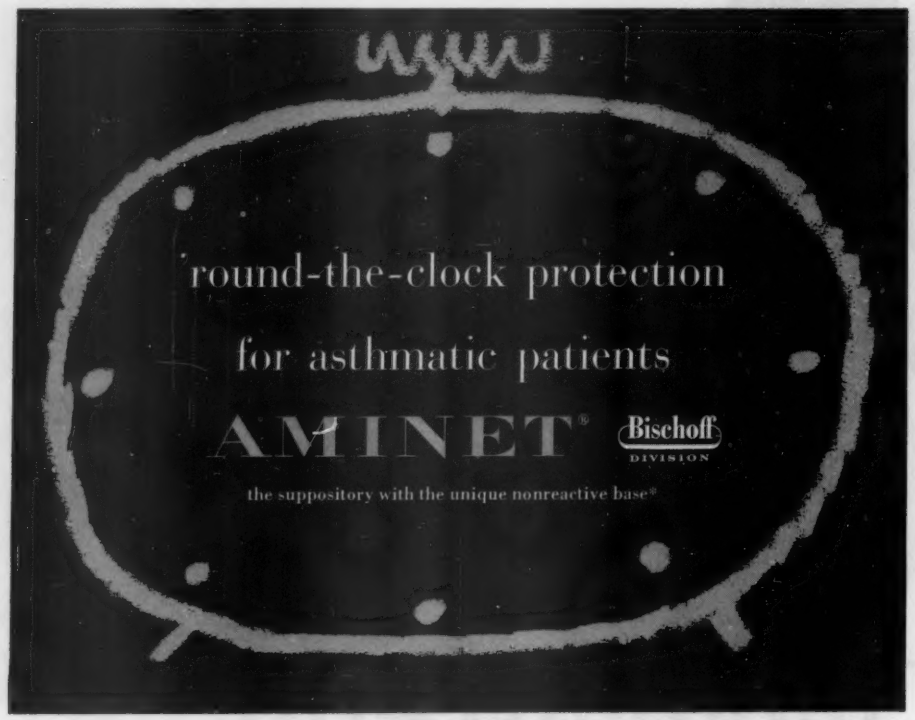
The rising incidence of bacterial resistance to various antibiotics constitutes a serious therapeutic problem. Many infections, once readily controlled, are now proving difficult to combat. Administration of CHLOROMYCETIN (chloramphenicol, Parke-Davis) is often useful in these cases because this notable, broad-spectrum antibiotic is frequently effective where other antibiotics fail.

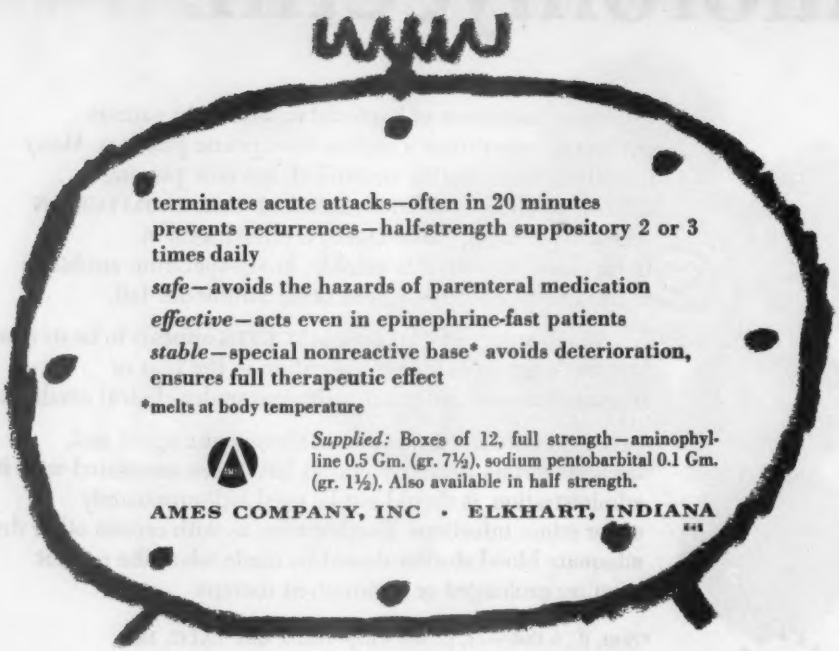
"...An advantage of CHLOROMYCETIN appears to be its relatively low tendency to induce sensitization in the host or resistance among potential pathogens under clinical conditions."*

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

*Pratt, R., & Dufrenoy, J.: Texas Rep. Biol. & Med. *12*:145, 1954.

PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN



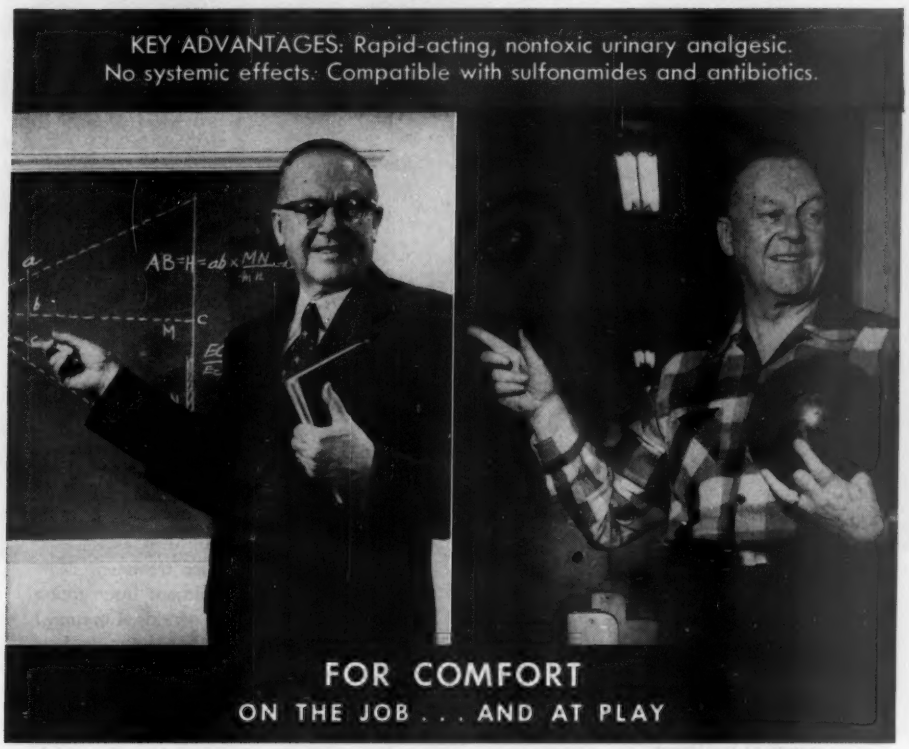

terminates acute attacks—often in 20 minutes
prevents recurrences—half-strength suppository 2 or 3 times daily
safe—avoids the hazards of parenteral medication
effective—acts even in epinephrine-fast patients
stable—special nonreactive base* avoids deterioration, ensures full therapeutic effect
*melts at body temperature
Supplied: Boxes of 12, full strength—aminophylline 0.5 Gm. (gr. 7½), sodium pentobarbital 0.1 Gm. (gr. 1½). Also available in half strength.
AMES COMPANY, INC • ELKHART, INDIANA

Entered as second-class matter, November 16, 1932, at the post office at Boston, Massachusetts, under the Act of March 3, 1879. Published weekly at 8 Fenway, Boston 15. Domestic, $8.00 per year.

Pyridium®

(PHENYLAZO-DIAMINO-PYRIDINE HCl)

Gratifying relief from urogenital discomforts *in a matter of minutes*


KEY ADVANTAGES: Rapid-acting, nontoxic urinary analgesic.
No systemic effects. Compatible with sulfonamides and antibiotics.
FOR COMFORT
ON THE JOB . . . AND AT PLAY

EFFECTIVE—In a study of 118 cases of pyelonephritis, cystitis, prostatitis and urethritis,[1] PYRIDIUM relieved or abolished dysuria in 95% of the patients and greatly reduced or abolished frequency in 85% of the cases.

NONTOXIC—PYRIDIUM produces rapid and entirely local analgesia of the urogenital mucosa. It may be administered in conjunction with sulfonamides or antibiotics to relieve distressing urogenital symptoms in the interval before the antibacterials can act.

PHYSIOLOGICAL—The soothing analgesic action of PYRIDIUM promotes relaxation of the sphincter mechanism of the bladder. This relaxation helps the patient to overcome urinary retention of spastic origin.

PSYCHOLOGICAL—PYRIDIUM imparts a characteristic orange-red color to the urine. This color-change gives patients added assurance of prompt action of the drug.

SUPPLIED: In 0.1 Gm. (1½ gr.) tablets, vials of 12 and bottles of 50, 500, and 1,000.

PYRIDIUM is the registered trade-mark of Nepera Chemical Co., Inc., for its brand of phenylazo-diamino-pyridine HCl. Sharp & Dohme, Division of Merck & Co., Inc., sole distributor in the United States.

SHARP & DOHME

PHILADELPHIA 1, PA.

DIVISION OF MERCK & CO., INC.

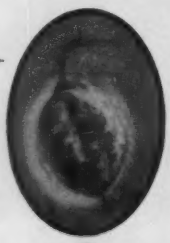
REFERENCE: 1. Kirwin, T. J., Lowsley, O. S., and Menning, J., Am. J. Surg. 62:330-335, December 1943.

EXPLOSION

OF TRICHOMONADS WITHIN 15 SECONDS OF CONTACT WITH VAGISEC liquid

A NEW AGENT, VAGISEC liquid, reaches deeply buried and surface trichomonads and explodes them within 15 seconds. No other trichomonacide has this effect.

The Davis technic. VAGISEC liquid is the trichomonacide developed as "Carlendacide" by Dr. Carl Henry Davis, well-known gynecologist and author, and C. G. Grand, research physiologist. Over 100 leaders in obstetrics and gynecology tested this new agent and reported "better than 80 per cent of cures among non-pregnant patients with one course of treatment."[1]



1. *Microphotograph (phase-contrast microscope) of a trichomonad*

2. *Trichomonad "exploded" within 15 seconds of contact with Vagisec liquid, diluted as douche*

Synergistic action. VAGISEC liquid combines a chelating agent to capture the calcium of the calcium proteinate, a wetting agent to remove lipid material and a detergent to denature the protein. Result, the trichomonad swells up and bursts.

Thorough penetration. VAGISEC jelly and liquid penetrate the cellular debris and mucoid material lining the vaginal wall and buried between the rugae. They reach trichomonads, hidden and surface.

Course of treatment. Dr. Davis recommends office treatment and home treatment and the use of both VAGISEC jelly and liquid. For "the small percentage of women who have an involvement of cervical, vestibular or urethral glands, other treatment will be required."[1]

Office treatment. Expose vagina with speculum. Wipe walls dry with cotton sponges and wash thoroughly for about three minutes with a 1:250 dilution of VAGISEC liquid. Remove excess with cotton sponges. There is no discharge or staining. Six office treatments are recommended.

Home treatment. Prescribe both VAGISEC jelly and VAGISEC liquid for home treatment. Patient inserts VAGISEC jelly each night and douches with VAGISEC liquid (1 teaspoonful to a quart of warm water) each morning except on office treatment days. Treatment continues without interruption through two menstrual periods. Continued douching with VAGISEC liquid two or three times a week helps to prevent re-infection.

Summary. VAGISEC liquid reaches deeply buried trichomonads and explodes them in 15 seconds. The Davis technic is a triple attack—office treatment, home treatment with jelly at night, and home treatment with liquid in the morning. VAGISEC jelly and liquid have been clinically tested and proved fast and effective. They are non-toxic.

1. Davis, C. H.: J.A.M.A. 157:126 (Jan. 8) 1955.

JULIUS SCHMID, INC. *Gynecological Division*

423 West 55th Street, New York 19, N. Y.

VAGISEC IS THE TRADE-MARK OF JULIUS SCHMID, INC., FOR PRODUCTS TO BE USED IN THE CONTROL OF VAGINAL TRICHOMONIASIS.

Active ingredients: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Boric acid, Alcohol 5% by weight.

ELECTRON PHOTOMICROGRAPH

Escherichia coli 36,000 X

Escherichia coli ("colon bacillus") is a Gram-negative organism
commonly involved in
urinary tract infections and peritonitis,
and is an important etiologic agent of otitis media, mastoiditis, enteritis,
and septicemia in infants.

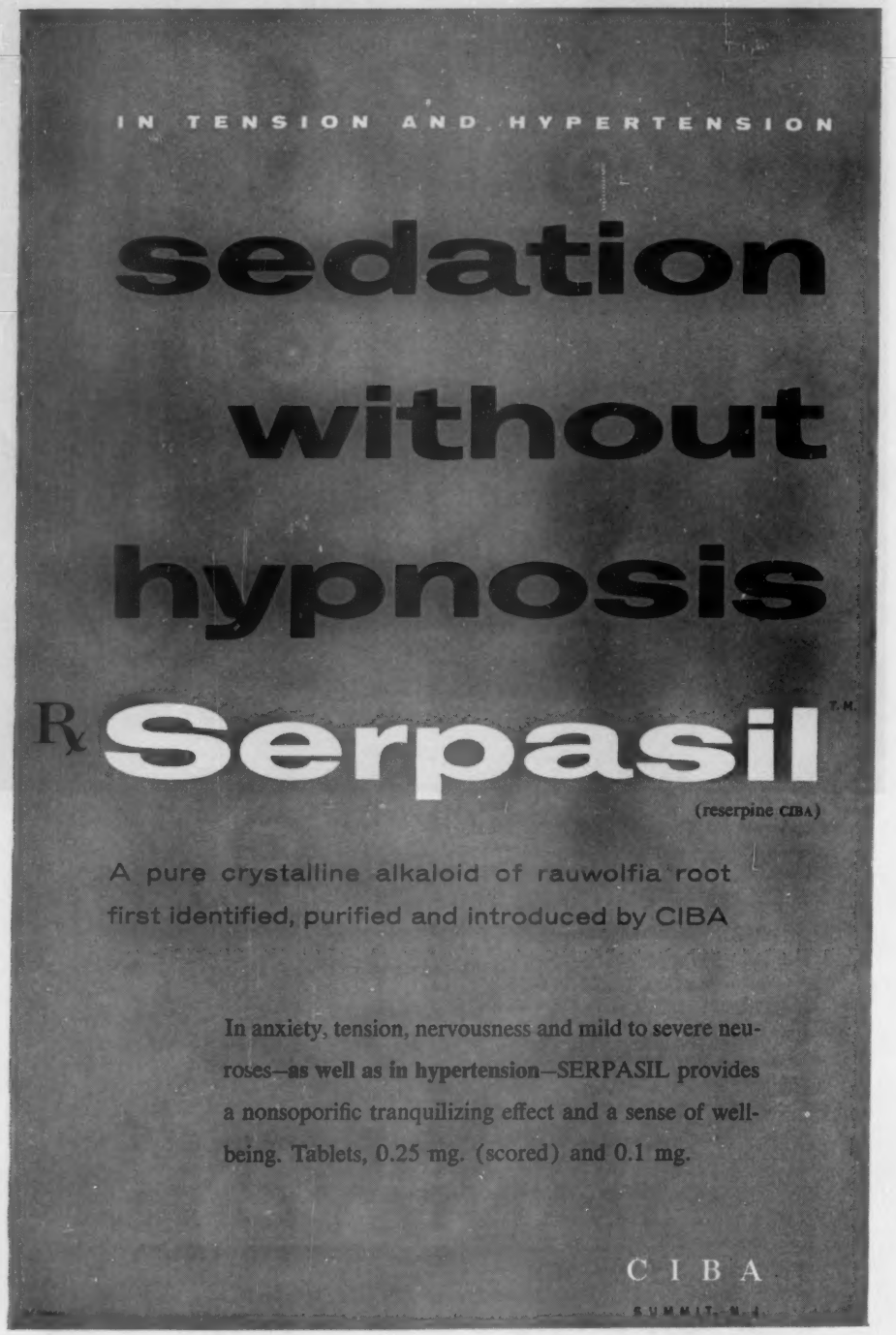
It is another of the more than 30 organisms susceptible to

PANMYCIN* HCl

100 mg. and 250 mg. capsules
125 mg./tsp. and 250 mg./tsp. oral suspension (Panmycin Readimixed)

Upjohn

*TRADEMARK, REG. U. S. PAT. OFF.


IN TENSION AND HYPERTENSION
sedation
without
hypnosis
℞ Serpasil T.M.
(reserpine CIBA)
A pure crystalline alkaloid of rauwolfia root
first identified, purified and introduced by CIBA
In anxiety, tension, nervousness and mild to severe neuroses—as well as in hypertension—SERPASIL provides a nonsoporific tranquilizing effect and a sense of well-being. Tablets, 0.25 mg. (scored) and 0.1 mg.
CIBA
SUMMIT, N. J.

PORTRAIT OF A POOR APPETITE . . .

When a mealtime masterpiece like this is part of your clinical picture,

prescribe TROPHITE*

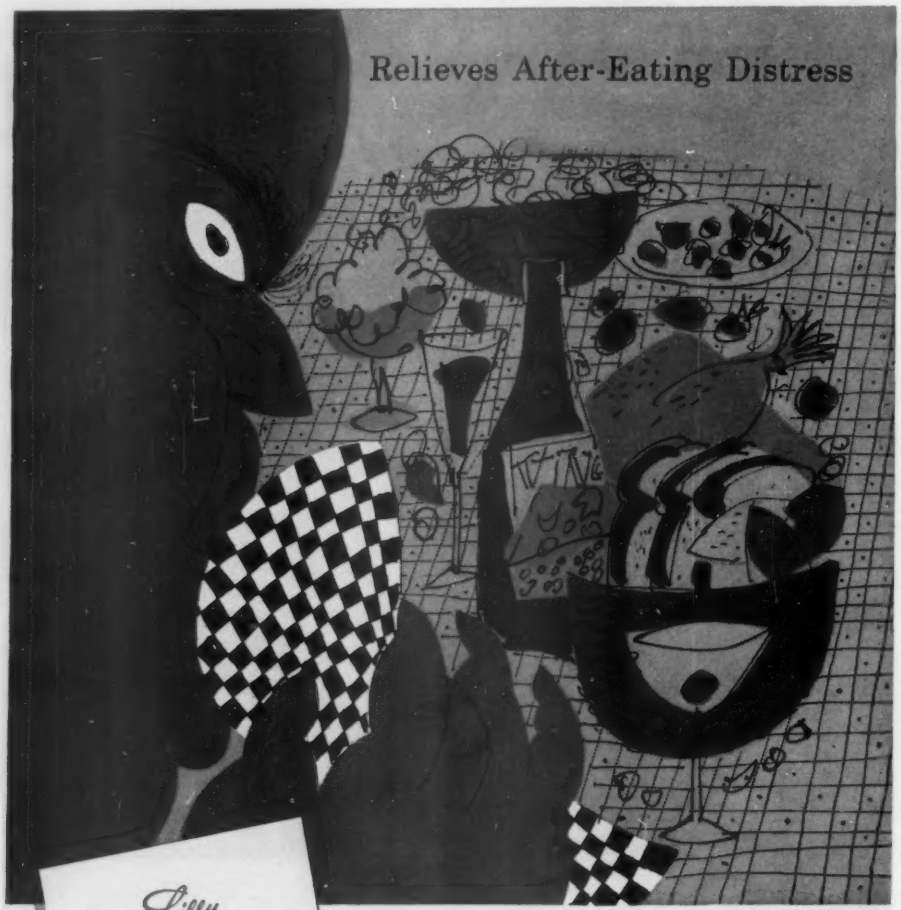
to stimulate appetite and promote growth.

Each tablet or teaspoonful (5 cc.) provides: 25 mcg. B_{12}; 10 mg. B_1

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

112



'Bilron'

(IRON BILE SALTS, LILLY)

A potent choleretic

Available in 2 1/2-grain and 5-grain pulvules.

In packages of 100, 500, and 5,000.

Dosage: Usually 5 to 10 grains daily with meals.

Under the priming influence of 'Bilron,' natural bile flow and concentration of bile acids are greatly increased. When symptoms include intolerance to fats, constipation, or flatulence, 'Bilron' offers effective, gratifying relief. Also, 'Bilron' dissolves in the small intestine at the optimal point for emulsification and absorption of fats.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

The New England
Journal of Medicine

Copyright, 1955, by the Massachusetts Medical Society

Volume 252 MARCH 31, 1955 Number 13

MANAGEMENT OF THE PREGNANT PATIENT WITH CARDIAC DISEASE*

WILLIAM HOROWITZ, M. D.†

BRONX, NEW YORK

ABOUT seventy-five years ago French physicians followed the dictum: the girl with heart disease should not marry; if married she should not bear children; and if she does bear a child she must not nurse. Today, with a better understanding of the physiologic cardiovascular changes during normal pregnancy, the physician can more properly evaluate and manage each patient so that many women with heart disease may have successful pregnancies.[1,2]

The maternal mortality has fallen largely because of adequate prenatal care, including the education of the patient. Statistics for Bronx County list 19 maternal deaths per 10,000 live births during 1940-1945 and 14.6 deaths during 1946 - 1951, a reduction of about 23 per cent. Maternal deaths due to cardiac diseases rank fourth after hemorrhage, anesthesia and toxemias. Table 1 reviews the data at Morrisania City Hospital. The sole cardiac death was in a thirty-eight-year-old Puerto Rican who was hospitalized during the fifth month of pregnancy as a para 4, gravida 5, in congestive heart failure due to rheumatic heart disease and mitral stenosis. She had responded well to digitalization, mercurial diuretics, rest and salt restriction, but left the hospital against advice. She was found dead at home during the eighth month of her pregnancy. Autopsy disclosed rheumatic mitral stenosis, bilateral hydrothorax and pulmonary edema. In 1949, 1 death due to active rheumatic fever during pregnancy was reported from this clinic.[3]

White[4] states that about 4 per cent of all pregnant women have symptoms referable to the cardiovascular system. Of these, half have apical systolic murmurs on a functional basis because of reversible cardiac dilatation and are therefore of no clinical importance. Thus, about 2 per cent of all pregnant women have organic heart disease. Table 2 summarizes the data from the Clinic but does not include direct admissions to the Hospital. The latter group of patients were seen and evaluated in consultation on the ward. Approximately half the patients referred had no organic heart disease. Of the others rheumatic heart disease was present in over 90 per cent. Congenital heart disease was found in 2 to 4 per cent, and the remainder had hypertensive, thyrotoxic, coronary and syphilitic heart disease.

*From the Prenatal Cardiac Clinic, and the Cardiovascular Service, with the co-operation of the Department of Obstetrics and Gynecology, Morrisania City Hospital.

†Clinical instructor in medicine, New York Medical College; chief, Prenatal Cardiac Clinic, and associate visiting physician, Morrisania City Hospital.

PHYSIOLOGIC VARIATIONS IN NORMAL PREGNANCY PREDISPOSING CARDIAC PATIENTS TO FAILURE

Increase in Cardiac Output

By means of cardiac-catheterization studies Hamilton[5] has shown that the cardiac output in normal pregnant women increases gradually after the tenth week. A maximum level about 27 per cent above that in the nonpregnant state is reached between the twenty-sixth and twenty-ninth weeks (from 4.5 to 5.7 liters), after which there is a slight fall. After the thirty-eighth week and until delivery cardiac output decreases almost to the level present before pregnancy.

Increase in Blood Volume

During normal pregnancy the blood volume increases about 50 per cent.[6] This maximum is reached by the thirty-sixth week, after which there is a gradual reduction. Little is known about alterations in the blood viscosity. Since the blood volume is already greatly increased, transfusion is particularly dangerous in pregnant cardiac patients. The blood pressure normally remains unaltered except for a slight fall during the second trimester, at the time of maximum cardiac output.

Retention of Salt and Water

During gestation there is a positive salt balance (retention of salt and water).[7] Water retention ceases during the last weeks of pregnancy, and many patients then lose large quantities of water.

Respiratory Reserve

In pregnant patients with heart disease the respiratory reserve is impaired both by reduction of vital capacity from the heart disease and by elevation of the diaphragm owing to the enlarging uterus.[8]

Classification of Cardiac Patients

After a diagnosis of organic heart disease has been established, patients are classified according to the criteria of Hamilton and Thomson.[9]

Unfavorable or Poor Risk

Patients in this group have a history of previous congestive heart failure, unless this occurred during a bout of acute rheumatic fever or was due to some extremely unusual exertion. Active rheumatic fever within a year of pregnancy and age above thirty-five years are also considered unfavorable. It is urged that if cardiac patients are to bear children they should do so between the ages of twenty-two and thirty years, when recurrences of rheumatic fever are least frequent.

Other contraindications to full-term delivery are atrial fibrillation; the presence of hemoptysis, which may signal increased pressure of the pulmonary circuit in mitral stenosis, with the likelihood of acute pulmonary edema (interruption of pregnancy with commissurotomy later has been advised[2]); striking enlargement of the cardiac chambers; and aortic stenosis or coarctation or dissection of the aorta, as well as congenital cardiac disease with cyanosis.

Table 1. *Data from the Department of Obstetrics and Gynecology, Morrisania City Hospital.*

Year	Mothers	Babies	Live Births	Maternal Deaths	
				Number	Cause
1950	1642	1663	1634	1	Rheumatic heart disease & mitral stenosis
1951	1929	1952	1923	1	Lower-nephron nephrosis
1952	2059	2089	2043	1 1	Eclampsia Hemorrhage
1953	1980	2007	1961	None	

Favorable Cases

There is no objection to full-term pregnancy if there is no history of heart failure. Usually, those cases are Class 1 and 2 cardiac disease according to the classification of the New York Heart Association. Similar cases are those of uncomplicated rheumatic disease of the mitral or aortic valves (except aortic stenosis).

Indications for Therapeutic Abortion

Always a difficult problem, the indications for therapeutic abortion in the cardiac patient can be resolved by means of the classification given above. If a patient in the group labeled "unfavorable or poor risk" becomes pregnant it is desirable to terminate the pregnancy as early as possible after cardiac compensation has been restored.

Until the third lunar month this may be accomplished by dilatation and curettage. Afterward, an abdominal hysterectomy, preferably with sterilization, is performed. Unless there are compelling obstetric indications, interruption should not be attempted after the sixth lunar month, when the cardiac load is reaching its maximum. The additional strain of an abdominal operation on the overburdened heart may cause failure and death. Furthermore, toward term the cardiac burden of pregnancy decreases considerably.

Management during Delivery

Prenatal Care

Jones[1] has aptly stated, "the mode of delivery is much less important than the condition of the patient at the time of delivery" (Table 3). Certainly, these patients should be on a low-salt diet. If all salt is omitted from cooking and from the table and salty foods avoided the sodium chloride in the diet can be brought down to about 3 gm. a day.

The weight gain should be limited to an average of 9.1 kg. (20 pounds) for the entire pregnancy.

Table 2. *Data from the Prenatal Cardiac Clinic.*

Year	Total Cases	Patients without Organic Heart Disease	Patients with Potential Rheumatic Heart Disease	Patients with Rheumatic Heart Disease	Patients with Congenital Heart Disease	Other Diseases in Referred Pregnant Patients	
						Number	Type
1951	101	51(50%)	36	10	1 (patent ductus arteriosus)	1 1 1	Toxemia Hyperthyroidism Thymolipoma
1952	95	56(59%)	32	4	1 (patent ductus arteriosus)	1 1	Toxemia Lupus erythematosus
1953	115	66(57%)	31	13	1 (patent ductus arteriosus) 1 (not definitely diagnosed — patent ductus or pulmonic stenosis)*	2 1	Hypertension Hyperthyroidism

*Patient refused angiocardiography.

The diet should be supplemented by vitamins, calcium and iron. Anemia should be corrected as indicated with ferrous sulfate, or folic acid or vitamin B_{12}, singly or in combination.

The patient must be cautioned against performing heavy physical work such as washing windows, scrubbing floors, pushing furniture and chasing after her children. She must learn to rest after each meal and to go to bed in midmorning and midafternoon and early at night. Exercise is contraindicated: calisthenics and hiking do not strengthen the heart.

Infection should be scrupulously avoided and vigorously treated when present. If teeth are to be extracted or other dental surgery to be performed, penicillin, 1,000,000 units daily, should be given at least two days before and after the procedure.

Frequent examination of the patient should include, in addition to routine urinalyses, recordings of weight and blood pressure and observation for early dyspnea, cough, hemoptysis, basal lung rales and pulse rate above 100. A simple objective sign is the vital capacity. If the task of appearing for prenatal visits is truly burdensome physically, they must be made less frequent or home calls arranged for.

Heart Failure during the Prenatal Period

The onset of failure may be heralded by a rapid weight gain due to salt retention and by elevation of the pulse above 110 and the respirations above 24. Treatment should be carried out, if possible, in a hospital and should in no way differ from that of a nonpregnant patient with cardiac disease. White[4] states that digitalis and quinidine do not affect the fetus unfavorably.

Acute pulmonary edema usually responds quickly to morphine, 20 mg., with atropine, 0.4 mg. Bloodless phlebotomy is accomplished by the application of tourniquets to the four extremities, one being released after fifteen minutes, with rotation by release and reapplication on another extremity every fifteen minutes thereafter. Oxygen by mask is helpful. In critical states rapid phlebotomy is performed with a 15-gauge needle in an accessible vein and the removal of at least 500 cc. of blood. Lanatoside C, 1.6 mg., is given intravenously.

Right-sided congestive heart failure may be treated in the usual manner by digitalization, rest, mercurial diuretics, ammonium chloride (4 to 6 gm. daily for three or four successive days each week) and rigid salt restriction.

The onset of cardiac failure during the prenatal period converts a previously "favorable" case to one in the "poor-risk" group. Only when compensation has been established is therapeutic abortion indicated and then, as pointed out above, at most up to the sixth lunar month. After that time the pregnancy should be permitted to continue, the method of delivery depending only on obstetric indications. The patient should be maintained on digitalis, a low-salt diet, ammonium chloride and mercurial diuretics as indicated, and followed preferably in the hospital.

Table 3. *Suggested Procedure in Rheumatic Heart Disease.**

Classification of New York Heart Association	Nonpregnant Patients	Pregnant Patients	
		1st pregnancy	subsequent pregnancies
"Favorable":			
Group 1 (no symptoms on any exertion) & Group 2 (cardiac symptoms only on great exertion)	No objection to pregnancy	Normal pregnancy under cardiac supervision, with delivery preferably in hospital	If no deterioration subsequent pregnancy carries no additional risk after full recuperation
"Unfavorable":			
Group 3 (cardiac symptoms on moderate exertion)	Advisability of pregnancy depends on facilities for supervision, circumstances of patient & value of child	Similar to "favorable" group, with prophylactic digitalization	Similar to above "favorable" group, but all factors carefully evaluated Prophylactic digitalization
Group 4 (cardiac symptoms at complete rest)	Pregnancy inadvisable	Termination early in pregnancy	After 6th lunar mo. pregnancy allowed to proceed to term, every effort being made to achieve compensation, with delivery according to obstetric indications

*Based on Jones.[1]

Bunim and Rubricus[10] report infant mortality as 30 per cent in mothers in congestive heart failure, in contrast to a rate of 9 per cent in patients with compensated disease and 7 per cent in those without cardiac disease.

Hamilton and Thomson[9] found the maternal death rate in "favorable" cases only slightly above that in noncardiac cases whereas in "poor-risk" patients the rate rose to 16.7 per cent. Therefore in this clinic, patients are digitalized prophylactically if their cardiac reserve is low.

Management during Delivery

Since the purpose of prenatal care is to bring the patient to the delivery table in a well compensated

state, the obstetrician is permitted to exercise his discretion regarding the type of delivery. He should be cautioned that, although normal labor is usually well tolerated, an arduous, protracted labor or difficult forceps delivery must be avoided. Patients with low cardiac reserve have become decompensated during or shortly after labor. In problem cases, when the question of a trial of labor arises, the obstetrician is advised to perform a cesarean section.

It may be noted at this point that coarctation or dissection of the aorta is a specific cardiac indication for cesarean section, since rupture of the aorta and other vascular accidents due to the hypertension have occurred during labor. There is no justification for performing a cesarean section merely for the convenience of sterilizing the patient.

Analgesics and hypnotics may be used as indicated during the first stage of labor. Oxygen by mask is helpful. Anoxia, quite frequent with nitrous oxide, must be avoided. The maternal pulse and respiratory rates should be noted almost continuously; early congestive heart failure may be manifested by a pulse persistently above 110 and respirations over 24. If the patient has not been previously digitalized, 1.6 mg. (8 cc.) of lanatoside C should be given immediately.

The second stage of labor should be made as short as possible, without undue manipulation. Adequate episiotomy with pudendal block and low forceps delivery are procedures of choice. If a decompensated patient is in labor an attempt should be made to keep her in the semiupright position and to give her oxygen continuously.

Pitocin may be given as in patients without cardiac disease to contract the uterus after delivery, except, of course, in cases of angina pectoris. A tight abdominal binder should be applied. The head of the bed should be so elevated on blocks that the neck-vein distention just disappears. This permits the patient to lie more comfortably in a straight bed without a sinking in of the chest and abdomen.[11]

Management during the Puerperium

Although it is now customary to allow the normal patient out of bed within twenty-four to forty-eight hours of delivery, it is urged that even the patient with "favorable" cardiac disease be kept in bed for at least a week, with the usual precautions against the development of thrombosis, such as deep breathing, movement from side to side and changes of position of the extremities. Lactation should be suppressed, since it may increase circulatory demands.

Congenital Cardiovascular Diseases

My experience with these cases has been limited. There were 3 patients with patent ductus arteriosus. In a fourth case no definite diagnosis could be made since the patient refused to submit to angiocardiography. All were carefully followed and had uneventful pregnancies and deliveries.

In the presence of patent ductus arteriosus, defect of the atrial or ventricular septum or Lutembacher's syndrome, in "favorable" cases and when the degree of cardiac enlargement is not severe, it is believed that the maternal mortality is no greater than that in "favorable" cases.[2]

The patients with cyanotic congenital cardiac disease usually do not reach maturity, and for the present purposes these cases are considered "unfavorable."

In patients with coarctation of the aorta the maternal mortality is reported as increased; cesarean section is recommended before the onset of labor.

Dissection of the Aorta

This lesion has been reported with and without coarctation in isolated cases; all must be considered "unfavorable."[12]

Coronary-Artery Disease

Although infrequent, single cases have been reported as successful deliveries after myocardial infarction.[13,14] Since the stress of pregnancy may precipitate another coronary occlusion or congestive heart failure or both[15] all these cases should be considered "unfavorable."

Hypertensive Cardiovascular Disease

Only 2 hypertensive patients were followed in this clinic, and both did well. These patients did not have eclampsia or pre-eclampsia, such cases being under the direct supervision of the obstetricians. Toxemia occurs more frequently in hypertensive than in normotensive patients.

Cases of hypertension may be classified as "favorable" or "unfavorable." The only difference in management is that the pregnancy must be terminated promptly when there is worsening of the hypertension with its sequelae.[16]

Subacute Bacterial Endocarditis

No cases of endocarditis were encountered in this clinic. Hamilton[2] believes that pregnancy may hasten the usual course of this illness, so that interruption is warranted. In rheumatic and congenital cardiac disease prophylactic antibiotic therapy should be given from the time of delivery through the puerperium.

"Post-Partal" Heart Disease

Sporadically, in the medical literature, this term is used to describe heart failure occurring in patients near term or in the puerperium.[17,18] Of unknown etiology and heretofore difficult of classification, these cases have been lumped with those of "Fiedler's myocarditis." There are no large series followed to autopsy since most reported cases have ended in recovery.

From the clinical and pathological descriptions available, these patients may have endocardial fibroelastosis, which, in adulthood, is compatible with long life.[19,20]

Conclusions

Knowledge of the normal physiologic cardiovascular changes in pregnancy permits the physician to manage successfully many more pregnant patients with cardiac disease. Proper diagnosis and evaluation of cases as "favorable" and "unfavorable or poor risk" are essential.

Interruption of pregnancy is rarely indicated for cardiac reasons except in the presence of hemoptysis due to a tight mitral stenosis, with increased pressure in the pulmonary circuit, active rheumatic fever, increasing hypertension, with its sequelae, and subacute bacterial endocarditis.

Prophylactic cesarean section is recommended for coarctation of the aorta and dissecting aneurysm, or to avoid a trial of long, arduous labor in a problem case with low cardiac reserve.

In "unfavorable or poor-risk" cases the patient should not become pregnant. Patients in the "favorable" group have almost as good a prognosis for a successful pregnancy as normal women.

2676 Grand Concourse

References

1. Jones, A. M. *Heart Disease in Pregnancy.* 76 pp. New York: Grune & Stratton, 1951.
2. Hamilton, B. E. Cardiovascular problems in pregnancy. *Circulation* **9**:922-933, 1954.
3. Horowitz, W., Gersh, E., and Burstein, J. Active rheumatic fever during pregnancy. *J.A.M.A.* **147**:42-44, 1951.
4. White, P. D. *Heart Disease.* Fourth edition. 1015 pp. New York: Macmillan, 1951.
5. Hamilton, H. F. H. Cardiac output in normal pregnancy as determined by Cournand right heart catheterization technique. *J. Obst. & Gynaec. Brit. Emp.* **56**:548-552, 1949.
6. Cohen, M. E., and Thomson, K. J. Studies on circulation in pregnancy: velocity of blood flow and related aspects of circulation in normal pregnant women. *J. Clin. Investigation* **15**:607-625, 1936.
7. Chesley, L. C. Weight changes and water balance in normal and toxic pregnancy. *Am. J. Obst. & Gynec.* **48**:565-593, 1944.
8. Anthony, A. J., and Hanson, R. Schlagvolumen und Minutenvolumen des Herzens am Ende der Schwangerschaft und nach der Entbindung. *Ztschr. f. Geburtsch. u. Gynäk.* **110**:1-8, 1934.
9. Hamilton, B. E., and Thomson, K. J. *The Heart in Pregnancy and the Childbearing Age.* 402 pp. Boston: Little, Brown, 1941.
10. Bunim, J. J., and Rubricus, J. Determination of prognosis of pregnancy in rheumatic heart disease. *Am. Heart J.* **35**:282-297, 1948.
11. Goldberger, E. *Heart Disease: Its diagnosis and treatment.* 651 pp. Philadelphia: Lea & Febiger, 1951. P. 623.
12. Furman, R. H., Kennedy, J. A., and Daniel, R. A., Jr. Coarctation of aorta complicated by dissecting aneurysm in pregnancy: report of case with survival studied by arteriography. *Am. Heart J.* **43**:765-772, 1952.
13. Klein, M. D., Fischl, A., and Shey, I. A. Pregnancy following coronary occlusion. *New York State J. Med.* **53**:575, 1953.
14. Brock, H. J., Russell, N. G., and Randall, C. L. Myocardial infarction in pregnancy: report of case with normal spontaneous delivery seven months later. *J.A.M.A.* **152**:1030, 1953.
15. Burstein, J. Unpublished data and personal communication.
16. Massey, F. C. *Clinical Cardiology.* 1160 pp. Baltimore: Williams & Wilkins, 1953. P. 1029.
17. Melvin, J. P., Jr. Post-partal heart disease. *Ann. Int. Med.* **27**:596-609, 1947.
18. Bashour, F., and Winchell, P. "Post partal" heart disease — syndrome? *Ann. Int. Med.* **40**:803-808, 1954.
19. Letteer, C. R. Endocardial fibroelastosis. *Ann. Int. Med.* **38**:573-582, 1953.
20. White, P. D., and Fennell, R. H., Jr. Endocardial fibro-elastosis with marked cardiac enlargement and failure in man who died at age of 71 after 15 years of angina pectoris and two years of congestive heart failure. *Ann. Int. Med.* **41**:333-342, 1954.

THE ASYMPTOMATIC ISOLATED PULMONARY NODULE*

Earle W. Wilkins, Jr., M.D.†

BOSTON

INCREASINGLY frequent reports[1,2] in the literature have emphasized the striking prevalence of malignant neoplasms among solitary pulmonary lesions. Such a frequency is not surprising, but it is not so widely known that these lesions may be completely asymptomatic even though malignant. Bugden,[3] Sharp and Kinsella,[4] Effler[5] and Storey, Grant and Rothmann[6] have called attention to this fact. They have all recommended exploratory thoracotomy when accepted measures have failed to establish a diagnosis.

Definition

The series described below includes 77 cases of asymptomatic pulmonary shadows from the records of the Massachusetts General Hospital from October 1, 1947, through October 1, 1954, in which an exact diagnosis was established by an operative procedure. The former date was chosen as representing approximately the opening of the chest survey unit at the Hospital. The series includes patients from both the public wards and the private services,‡ the initial roentgenograms being taken in a mass survey, as part of a routine examination or as a step in the investigation of a complaint unrelated to the pulmonary lesion.

The cardinal criterion for these lesions has been the lack of symptoms. In addition they have fulfilled certain roentgenographic interpretative criteria as seen on the 36-by-43-cm. (14-by-17-in.) film: round or oval in appearance, circumscribed, solitary, solid in appearance, homogeneous or containing calcium and located within lung parenchyma as far as could be determined by evaluation of the roentgenogram. These are approximately the requisites propounded by Storey, Grant and Rothmann[6] in their definition of the so-called "coin" lesion. Limitation by size, however, has been omitted as arbitrary in the consideration of symptomless lesions. The inclusion of most larger solitary lesions is limited by their symptomatic nature.

Size is mentioned for possible comparison with other series. Sixty-nine of the 77 lesions were smaller

*From the Department of Surgery, Massachusetts General Hospital.

†Assistant in surgery, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

‡Patients of Drs. Edward D. Churchill, Richard H. Sweet and J. Gordon Scannell.

than the 5-cm. limit imposed by Storey, Grant and Rothmann.[6] Of the 8 lesions that were larger, 3 were 6 cm. in diameter, the other 5 varying up to a maximum of 12 cm. Of the 8 lesions larger than 5 cm., 5 were carcinomas, and 3 benign, a higher proportion of malignant lesions than in the series as a whole.

Specifically excluded from this series are mediastinal, diaphragmatic and chest-wall tumors, any lesion with associated atelectasis and the Ghon tubercle complex.

Finally, these cases come from a large general hospital caring for patients of both sexes and all ages, including a liberal number with tuberculosis. If there is any element of the population not proportionately represented, it is in the male group of military age because of the proximity of Veterans Administration and military hospitals. Storey, Grant and Rothmann[6] have given an excellent review of the significance of these factors in the final frequency of neoplasm in various series.

TABLE 1. *Asymptomatic Pulmonary Lesions.*

TYPE OF LESION		NO. OF CASES
Carcinoma, primary		27(35%)
Adenocarcinoma	11	
Squamous-cell	7	
Undifferentiated	6	
Adenomatosis	2	
Oat-cell	1	
Tuberculosis		18(23%)
Hamartoma		11(14%)
Benign tumor, other		10(13%)
Cyst	4	
Mesothelioma	3	
Adenoma	2	
Neurofibroma	1	
Carcinoma, metastatic		6(8%)
Renal-cell	3	
Colon	3	
Inflammatory processes		5(7%)
Granuloma	2	
Paraffinoma	1	
Hyperplastic lymph node	1	
Fibrin body	1	
Totals		77

ANALYSIS OF CASES

The wide range of diagnoses in this group is enumerated in Table 1. A diagnosis of neoplastic disease was established in 33 cases (42.8 per cent of the total), including 27 primary carcinomas of the lung and 6 metastatic lesions. The 27 primary neoplasms included 11 adenocarcinomas, 7 squamous-cell carcinomas, 6 undifferentiated carcinomas, 2 pulmonary alveolar adenomatoses (or alveolar-cell carcinomas) and 1 oat-cell carcinoma. The 6 metastatic lesions comprised 3 renal-cell carcinomas and 3 colon adenocarcinomas, including 1 each from the cecum, the transverse colon and the sigmoid colon. The diagnosis of 3 metastatic lesions was first established by thoracotomy; the other 3 were discovered six, twelve and twelve years respectively after the primary surgical procedures. Asymptomatic metastatic lesions appearing within an arbitrary period of less than five years were not included, so that the series would not be unduly weighted with early recurrent malignant neoplasms.

Some form of tuberculosis was reported in 18 cases (23.4 per cent). In 13 a so-called tuberculoma was discovered, and in the remaining 5 the pathologist described only circumscribed fibrocaseous disease.

The diagnosis of hamartoma was made in 11 cases (14.3 per cent). In each of these the lesion was peripheral, situated immediately beneath the pleura. In 1 case there were actually 2 hamartomas lying adjacent to one another within a basal segment of the left lower lobe.

Among the other benign tumors, some form of cyst was found in 4 cases. These included 2 simple cysts of the peripheral portion of the lung, 1 bronchogenic cyst and 1 cyst formed in the process of an intralobar sequestration. The other 6 benign tumors comprised 3 mesotheliomas of the discrete, localized form,[7] 2 bronchial adenomas and 1 neurofibroma of lung parenchyma.

Finally, there were 5 miscellaneous pathologic entities, all inflammatory. Two of these were granulomatous nodules in which no tubercle bacilli or other causative agents could be isolated. Another was a typical example of lipoid pneumonia or paraffinoma. Another unusual diagnosis was hyperplasia of an intralobar lymph node within the substance of the right lower lobe. This was known to have been present unchanged, as shown by x-ray study, for six years. The last was a pleural fibrin body attached to both the parietal and the visceral pleuras that had seemed roentgenographically to be within the lung.

OPERATIONS

Table 2 enumerates the types of operations employed. In general, it has been customary to carry out the minimal procedure required for removal of the nodule, to obtain a diagnosis if possible by gross inspection or frozen section, and then to proceed with more extensive extirpation as indicated. There were 5 pneumonectomies, 32 lobectomies, 8 excisions of one or more segments of a lobe and 30 local excisions (wedge excisions or simple enucleations). Only

1 case of carcinoma was explored in which mediastinal metastases prohibited removal. (There were 5 cases in all in which mediastinal lymph nodes were found to contain carcinoma.) The final operative procedure listed in Table 2 was unusually interesting. This case illustrates the natural history of a carcinoma of the lung that appeared first as a symptomless roentgenographic shadow.

CASE 1. J.N., a 64-year-old man, was first hospitalized from May 21 to July 18, 1947, because of an ulcerating lesion in the stomach diagnosed as carcinoma. Accordingly, subtotal gastrectomy was performed, with splenectomy, partial pancreatectomy and resection of the transverse colon. The pathological diagnosis, however, was gastric ulcer. A roentgenogram of the chest taken during this hospital admission was clear.

He reported to the Out Patient Department on November 30, 1949, because a survey chest film had shown an abnormal density in the right midlung field. He had no symptoms. Hospital admission was advised but was refused. He was not seen again until February 24, 1951, when he again reported to the Out Patient Department because of cough with blood-streaked sputum that he had first noticed on January 22. X-ray examination of the chest demonstrated a lobulated density measuring 7.5 cm. in diameter occupying the posterior segment of the right upper lobe. Hospital admission was again advised and once again refused.

He was finally admitted to the hospital on December 26, 1952, because of pain and persistent hemoptysis. On roentgenographic examination an abscess was found, probably from dissolution of carcinoma. Extirpation was considered unwise. An aspiration biopsy failed to produce a diagnosis. No definitive therapy was possible, and he was discharged on January 10, 1953.

The increasing severity of his symptoms led to his readmission on March 21. Drainage of the abscess was chosen as a method for relief of some of the symptoms. This made it possible to establish a diagnosis of carcinoma of the lung. He was ultimately discharged on May 5 and was last seen in the follow-up clinic on May 28, 1953.

TABLE 2. *Operations.*

OPERATION	TOTAL CASES	CASES OF PRIMARY CARCINOMA	CASES OF METASTATIC CARCINOMA	CASES OF TUBERCULOSIS	CASES OF HAMARTOMA	CASES OF BENIGN TUMOR	CASES OF INFLAMMATORY PROCESS
Pneumonectomy	5	5	—	—	—	—	—
Lobectomy	32	19	3	5	1	2	2
Segmental excision	8	1	1	5	—	1	—
Local excision	30	—	2	8	10	7	3
Exploration & biopsy	1	1	—	—	—	—	—
Drainage of malignant abscess	1	1	—	—	—	—	—

There were 2 operative (hospital) deaths in the series, representing an over-all mortality of 2.6 per cent.

AGE DISTRIBUTION

Table 3 demonstrates the occurrence of diagnoses by decades. The majority of cases were distributed quite evenly throughout the age groups. The obvious exception was the limitation of carcinoma to the later decades. Only 2 of 27 cases of primary lung carcinoma occurred before fifty years of age. One was in a forty-one-year-old man with pulmonary alveolar adenomatosis. The other patient was a man aged forty-six with an adenocarcinoma. Of the 27 lung carcinomas, all but 4 occurred in male patients. Over the age of fifty 50 per cent of asymptomatic circumscribed lesions removed surgically were primary carcinomas of the lung. If metastatic lesions are included 58 per cent of these patients over fifty years of age proved to have carcinoma.

TABLE 3. *Age Distribution.*

LESION	20-29 YR. OF AGE	30-39 YR. OF AGE	40-49 YR. OF AGE	50-59 YR. OF AGE	60-69 YR. OF AGE	70-79 YR. OF AGE
	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS	NO. OF PATIENTS
Primary carcinoma	—	—	2	12	9	4
Tuberculosis	2	4	6	4	2	—
Hamartoma	—	2	2	4	3	—
Metastatic carcinoma	—	1	1	1	3	—
Cyst	1	—	1	2	—	—
Mesothelioma	—	—	1	1	1	—
Bronchial adenoma	—	1	—	1	—	—
Granuloma	—	—	1	—	1	—
Neurofibroma	—	—	—	1	—	—
Paraffinoma	—	—	1	—	—	—
Hyperplastic node	—	1	—	—	—	—
Fibrin body	—	—	—	—	1	—
Totals	3	9	15	26	20	4

Another interesting feature of this analysis by decades is the frequency of tuberculosis, which, although decreasing in the later decades, was present as late as sixty-four years of age. It cannot be discounted, therefore, on an age basis. A graphic comparison of the relative prevalence by decades of these two most frequent diagnoses is presented in Figure 1. The rate of tuberculosis gradually declines through

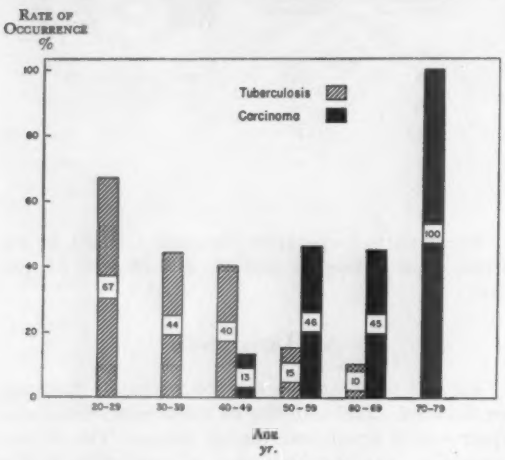


Figure 1. *Relative Frequency of Tuberculosis and Carcinoma by Decades.*

the decades whereas that of carcinoma rises sharply until, in the last decade represented, all cases prove to be primary carcinomas of the lung. Hamartomas, about whose etiology little is known, show a uniform distribution throughout the middle decades.

Diagnostic Procedures

With asymptomatic pulmonary lesions it is universally recognized that few diagnostic procedures are of real benefit in the preoperative definition of the pathologic process. The history is of no assistance. Physical examination is seldom helpful because discrete densities completely surrounded by aerated pulmonary tissue are not detectable by percussion nor with the stethoscope. Of the specific diagnostic studies a few were of occasional help in this series of patients. These included bronchoscopy, cytologic and bacteriologic study of sputum and washings obtained at bronchoscopy and comparison of previous roentgenograms (Table 4).

Bronchoscopy, performed in 33 cases, gave positive diagnostic assistance in only 3. In all 3 the diagnosis of carcinoma was ultimately established. In 2 cases gross findings were suggestive of carcinoma although confirmatory biopsy was not obtained. The third represented the only biopsy showing carcinoma. This relative lack of help from bronchoscopy was not unexpected because the lesions in this group were almost exclusively peripheral and not readily accessible to bronchoscopic visualization. Only for special indications, such as central location or to obtain bronchoscopic washings, was bronchoscopy considered beneficial in this group of cases.

It was hoped that the cytologic examination of sputum and bronchoscopic washings might prove to be valuable as a diagnostic measure. In the 32 patients whose sputum was examined by the Papanicolaou method, there were only 3 reports of malignant cells. One of these subsequently proved to be falsely positive in a case of tuberculosis. As with bronchoscopy the failure to find tumor cells was regarded as a manifestation of the peripheral location of these tumors with their remoteness from larger bronchi.

Examination of sputum for tubercle bacilli was made in 11 patients of the 18 with the proved diagnosis of tuberculosis. In none of these were tubercle bacilli found.

Of the 77 patients only 16 had previous roentgenograms of the lungs that were available for comparison. Seven had carcinoma; in 4 of these the previous examination had been negative. This determination is a most helpful diagnostic aid. If, in patients over fifty years of age, a lesion appears in lung fields that have previously been clear radiologically, the diagnosis of carcinoma is almost certain. The other 3 patients with carcinoma had previously had abnormal roentgenograms and had been followed for varying lengths of time before surgical exploration. Of the 9 remaining patients the previous x-ray study

Table 4. *Diagnostic Studies.*

Procedure Employed	No. of Cases	Procedure of Positive Assistance	False-Positive Result
		No. of cases	No. of cases
Bronchoscopy	33	3	
Papanicolaou examinations of sputum & bronchial washings	32	2	1
Comparison of previous roentgenograms	16	4	
Sputum examination for tubercle bacilli	11	0	
Laminography	2	0	
Angiography	1	1	

was negative in 6, with earlier evidence of tuberculosis in 3.

In only 2 patients was laminography employed, and in neither of these was it of any assistance in diagnosis. This procedure has been reported to be of value in the demonstration of minute calcification in tuberculous lesions.[8] Calcification is usually not seen in carcinoma except for that accompanying tuberculosis.

Angiography was employed in a case of carcinoma in which a shadow widening the opposite side of the

superior mediastinum was demonstrated to be vascular and not caused by metastatic lymph nodes.

Intradermal sensitivity tests were of no assistance in this series. Aspiration biopsy was not employed, except in Case 1, because of the dangers of dissemination of carcinoma, pneumothorax and hemorrhage.

Discussion

It is apparent that no investigative procedure is of consistent value in diagnosis. As has been repeatedly pointed out, the feasibility of thoracotomy for diagnosis has been demonstrated. Improvements in technics of anesthesia, surgery and care of the patient, as well as the availability of whole blood and antibiotics, have contributed to the safety of exploratory thoracotomy. With the high prevalence of carcinoma in this group of patients, the seemingly radical advocacy of thoracotomy as a diagnostic measure is actually the safest course to follow. Table 5 presents figures from comparable series reported in the literature. This tabulation demonstrates carcinoma in 30 per cent despite the lower average age in all other series in which such a figure is listed.

The 2 deaths in this series of 77 patients occurred in patients who had carcinoma of the lung. One was attributable to the extirpative surgery necessary to eradicate the disease so that there was insufficient aerating lung tissue to tide the patient over the stress of the immediate postoperative period; it was not due to the exploration for diagnosis. The other was presumably the result of a pulmonary embolism, a possible complication in all types of surgery. There was no morbidity resulting from exploration alone. There was only 1 complication in the entire group: an empyema resulting from a leaking bronchial stump after lobectomy for carcinoma.

Thus, an approach comparable to the management of breast lesions is suggested. Unless there is some unusual contraindication these symptomless pulmonary lesions should be handled by thoracotomy, biopsy and further appropriate extirpation as justified by the situation.

The hazards of the only other possible approach — that of periodic observation by roentgenogram — are demonstrated by the following case from this series.

Case 2. C. B., a 64-year-old man, was first hospitalized in December, 1946, for removal of a lipoma of the ascending colon. At this admission routine x-ray study of the chest demonstrated a discrete, homogeneous lesion in the left upper lobe that was causing no symptoms. During 5 subsequent surgical admissions for incisional and bilateral inguinal hernias the shadow appeared to increase slowly in size. Because of this, at a 7th admission in September, 1951, the left upper lobe was resected. The pathological report was adenocarcinoma, Grade 1, with uninvolved hilar lymph nodes. At the time of its removal, 4 years and 9 months after its detection, the lesion was still symptomless. For 2 years after lobectomy the patient did well, but then recurrent disease appeared in the left hemithorax. At last report, 9 months later, he was confined to a nursing home with widespread recurrence.

One cannot know the ultimate result in this case if lobectomy had been performed when the lesion was first detected. A more favorable outcome is possible. In his series of solitary lung neoplasms Harrington[12] described 7 patients originally without symptoms who, by the time of exploration after varying intervals of indecision, were found to have inoperable carcinomas.

Attention must be called to contraindications to the adoption of a policy of exploration for all asymptomatic pulmonary lesions. These include advanced age, extensive associated pulmonary disease, severe cardiac disease and severe asthma. Such factors, along with the relative skill of the surgeon and his team, must temper the decision for exploration in certain cases.

Table 5. *Frequency of Carcinoma Reported in Various Series.*

Year	Author	Total Cases	Average Age	Cases of Carcinoma*	Cases of Tuberculosis
			yr.		
1948	Effler et al.[9]	24	35	4(16.7%)	7
1950	Bugden[3]	8	37	4(50.0%)	1
1950	Sharp & Kinsella[4]	53		15(28.3%)	21
1951	Effler[5]	16	50	7(43.8%)	8
1951	Abeles & Ehrlich[10]	21		8(38.1%)	5
1953	Hood et al.[11]	81		18(22.2%)	36
1953	Storey et al.[8]	40	33	7(17.5%)	28
1954	Present series	77	53	33(42.8%)	18
Totals		320		96(30.0%)	124

*Only asymptomatic patients included.

No attempt has been made in this series to determine the ultimate survival in 27 patients with primary pulmonary carcinoma. Insufficient time has elapsed to permit informative deductions regarding survival rates. It is hoped that patients whose carcinomas are removed in an asymptomatic phase will have an improved prospect of permanent cure. That 5 patients already had lymph-node metastases at the hilus of the lung suggests that there will be no difference in a certain percentage of cases. Nevertheless, at present, prompt excision while a carcinoma is in a symptomless phase offers the greatest hope for its cure. Because there is no conclusive method for differentiating a malignant from a benign asymptomatic shadow, exploration must be considered in all cases in which there is no real contraindication.

Summary and Conclusions

In a series of 77 incidental solitary pulmonary lesions there were 33 cases of carcinoma, of which 27 were primary and 6 metastatic from other organs.

In patients over fifty years of age 29 out of 50 lesions (58 per cent) proved to be carcinoma.

Exploration of the thorax for diagnosis presents a negligible morbidity and is advocated in these cases. The results of expectant management may be tragic.

References

1. Davis, E. W., and Klepser, R. G. Symposium on diagnosis and treatment of premalignant conditions: significance of solitary intrapulmonary tumors. *S. Clin. North America* **30**:1707-1715, 1950.
2. O'Brien, E. J., Tuttle, W. M., and Ferkaney, J. E. Management of pulmonary "coin" lesion. *S. Clin. North America* **28**:1313-1322, 1948.
3. Bugden, W. F. Asymptomatic and circumscribed lesions of chest. *Am. Rev. Tuberc.* **62**:512-517, 1950.
4. Sharp, D. V., and Kinsella, T. J. Significance of isolated pulmonary nodule. *Minnesota Med.* **33**:886-888, 1950.
5. Effler, D. B. Solitary lung tumors. *Am. Rev. Tuberc.* **63**:252-254, 1951.
6. Storey, C. F., Grant, R. A., and Rothmann, B. F. Coin lesions of lung. *Surg., Gynec. & Obst.* **97**:95-104, 1953.
7. Brown, W. J., and Johnson, L. C. Postinflammatory "tumors" of pleura. *Mil. Surgeon* **109**:415-424, 1951.
8. Mahon, H. W., and Forsee, J. H. Surgical treatment of round tuberculous pulmonary lesions (tuberculomas). *J. Thoracic Surg.* **19**:724-740, 1950.
9. Effler, D. B., Blades, B., and Marks, E. Problem of solitary lung tumors. *Surgery* **24**:917-928, 1948.
10. Abeles, H., and Ehrlich, D. Single circumscribed intrathoracic densities. *New Eng. J. Med.* **244**:85-88, 1951.
11. Hood, R. T., Jr., Good, C. A., Clagett, O. T., and McDonald, J. R. Solitary circumscribed lesions of lung: study of 156 cases in which resection was performed. *J.A.M.A.* **152**:1185-1192, 1953.
12. Harrington, S. W. Surgical treatment of circumscribed intrathoracic lesions: lesions found on routine thoracic roentgenologic examinations with absence of subjective symptoms. *Dis. of Chest* **19**:255-270, 1951.

EFFECTS OF ANTICHOLINERGIC DRUGS ON PEPSIN PRODUCTION AND UROPEPSINOGEN EXCRETION*

Harold M. Silver, M.D.,† Helio Pucci, M.D.,‡ and Thomas P. Almy, M.D.§

NEW YORK CITY

THE effects of anticholinergic drugs on gastric function have usually been measured by radiologic studies to determine decrease in motility and tone, or by intubation technics to determine the decrease in volume and acidity of the gastric juice. The purpose of the present study was to determine the effects of these agents on the secretion of pepsin. Because we were able to show significant depression of pepsin output in acute experiments, we explored the use of uropepsinogen excretion as a measure of long-term anticholinergic effects. The rationale for this method is the fact that the gastric cells producing pepsin secrete pepsinogen into the blood stream, as well as into the gastric lumen. A portion of the circulating pepsinogen is then passed in the urine. Janowitz and Hollander[1] have pointed out that, under basal conditions, the partition of pepsinogen between urine and gastric juice is approximately as 1 is to 99, and Gray et al.[2] have shown a similar ratio under conditions of stimulation.

Method

Ten subjects, 9 male and 1 female, all of whom had active duodenal ulcers, were intubated after fasting overnight. Gastric juice was collected by continuous manual aspiration and pooled in fifteen-minute collection periods. It was promptly refrigerated until analysis. After a one-hour collection of basal secretion, methantheline bromide,¶ in a dosage of 0.2 mg. per kilogram of body weight, was administered intravenously over a five-minute period. Fifteen minutes after the beginning of the injection, collection for a second hour was begun. On each fifteen-minute specimen, measurements were made of volume and of free and total acid by sodium hydroxide titration, with the use of Töpfer's reagent and phenolphthalein as indicators. Pepsin was measured by the method of West, Ellis and Scott,[3] described below. In some of the periods after administration of methantheline the small volume of secretion required pooling of several specimens to attain a volume adequate for analysis.

For the uropepsinogen studies 8 male subjects, 6 of whom were normal and 2 of whom had duodenal ulcer (active in subject 4 and quiescent in subject 8) received propantheline‖ by mouth, 30 mg. three times daily and 45 mg. at bedtime. No other medication was administered. Timed nightly urine collections were made during a control period of seven or more days, during a similar period of propantheline administration and during a subsequent control period. For nocturnal collections the subject emptied the bladder on retiring, recorded the time and discarded the specimen; he then collected all urine voided throughout the night. On rising he emptied the bladder, added the specimen to that collected during the night and recorded the time. Aliquots of the nocturnal samples were analyzed by the method of West and his associates.[3] This consists of conversion of pepsinogen to pepsin by acidification and incubation at 37°C. for an hour. Urine so activated is diluted with distilled water and buffered at pH 4.9. Homogenized milk,

*From the Department of Medicine, New York Hospital-Cornell Medical Center.

Presented in part at a meeting of the Eastern Section of the American Federation for Clinical Research, Boston, January 4, 1954.

Aided by a grant from G. D. Searle and Company, Chicago.

†Fellow in cardiopulmonary diseases, Barton Memorial Division of Jefferson Medical College Hospital, Philadelphia.

‡Fellow of the Kellogg Foundation and the American College of Physicians.

§Associate professor of medicine, Cornell University Medical College; visiting physician and director, Second (Cornell) Medical Division, Bellevue Hospital.

¶Kindly supplied as Banthine by Dr. I. C. Winter, of G. D. Searle and Company, Chicago.

‖Kindly supplied as Probanthine by Dr. I. C. Winter, of G. D. Searle and Company, Chicago.

also buffered at pH 4.9, is the substrate, and the time for peptic coagulation of casein by the activated urine is determined. From this time (t), the volume of activated urine added (v), and the hourly urine volume (V), the pepsin excretion in units per hour may be calculated by the formula given by West et al.:

$$\text{Units/hr.} = \frac{V}{10v} \cdot \left(\frac{100}{t}\right)^{1.32}$$

The unit so defined is equivalent to 0.26 microgm. of crystallized pepsin. To adapt this method to determination of gastric pepsin, gastric juice was diluted 1:100 with distilled water before activation, and the values found on this dilution multiplied by 100. The time-concentration curve was identical to that of urine. To calculate the number of units per fifteen-minute sample, V in the formula expressed above was changed to cubic centimeters of gastric juice per fifteen-minute period. The values for each of four fifteen-minute periods before and after intravenous administration of methantheline were added to give units per hour (Table 1). All pepsin determinations were done in triplicate.

Results

Gastric Secretory Changes

In every case the output of gastric pepsin promptly and strikingly decreased after intravenous administration of methantheline. The mean pepsin value in the fifteen-minute period immediately before injection was 4301 units. In the fifteen-minute period of which injection occupied the first five minutes, the mean value was 1427 units, and in the first complete fifteen-minute period after the injection, the mean was 523 units (Table 2). The values obtained in the hour after the injection period averaged 21.1 per cent of control, with a range of 7.6 per cent to 41.9 per cent (Table 1). The volume of gastric juice decreased in every case, the mean value being 20.8 per cent of control, with a range of 4.9 per cent to 39.4 per cent. Free acid output was reduced to values averaging 16.1 per cent of control, with a range of 0 to 49.0 per cent of control. The decreases in volume and in pepsin (Fig. 1) were roughly proportional; thus pepsin *concentration* was *not* altered in any consistent fashion. In every case methantheline produced dryness of the mouth during or shortly after the injection. Blurring of vision was occasionally seen.

TABLE 1. *Effects of Intravenous Administration of Methantheline on Gastric Secretion.*

Subject No.	Pepsin		Changes after Banthine		
	Before Banthine	After Banthine	Pepsin	Volume	Acid
	units/hr.	*units/hr.*	*% of control*	*% of control*	*% of control*
1	25,760	4,107	15.9	21.9	13.3
2	26,420	6,205	23.5	22.0	8.1
3	12,792	4,145	32.4	35.6	49.0
4	5,308	665	12.5	14.0	0
5	17,868	3,367	18.8	33.3	38.5
6	6,723	1,065	15.8	10.6	0
7	3,806	289	7.6	4.9	12.0
8	13,191	1,094	8.3	4.9	2.4
9	7,294	2,537	34.7	21.6	21.8
10	12,569	5,267	41.9	39.4	16.2
Means	13,173	2,874	21.1	20.8	16.1

TABLE 2. *Prompt Decrease in Gastric Pepsin Secretion after Intravenous Administration of Methantheline.*

Subject No.	Pepsin		
	Last period before banthine	Period including injection	First complete period after injection
	units/ 15 min.	*units/ 15 min.*	*units/ 15 min.*
1	8,240	7,080	1,640
2	9,560	384	0
3	4,044	1,878	1,116
4	1,397	423	362
5	5,084	2,132	340
6	2,794	192	192
7	1,158	110	67
8	3,333	967	292
9	3,217	480	497
10	4,179	622	727
Means	4,301	1,427	523

Uropepsinogen

The results are presented in Table 3, which shows the mean value for each control period and for the period on propantheline. These values exclude the first day on propantheline and the first day of the second control period to allow for equilibration. In the individual case the control mean (fifth column of Table 3) was not always the mean of the values for the two control periods, because the number of observations during each control period was not always the same. In each case the mean hourly rate of uropepsinogen excretion was less during propantheline administration than during each of the two control periods, averaging 78 per cent of control, with a range of 63 per cent to 88 per cent. This difference is statistically significant ($p<0.01$).

The results of a typical experiment are shown in Figure 2*A*. Of note is the considerable variation in values from day to day. Despite some overlap the

decrease induced by propantheline is evident, and is confirmed by the return to control levels after administration, which exceed those of the first control period. In another case (Fig. 2*B*) propantheline distinctly lowered the values, but in contrast with the preceding case, the values in the second control period were lower than those in the first control period.

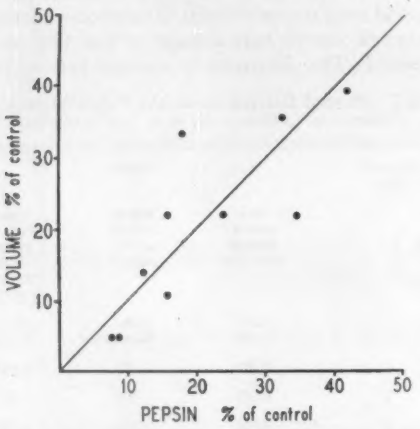


FIGURE 1. *Decrease of Volume of Gastric Secretion, Compared with Decrease of Gastric Pepsin, after Intravenous Administration of Methantheline.*

DISCUSSION

The studies on gastric pepsin confirm certain observations of Whitrock and his associates,[4] which were reported in abstract while our work was in progress. They found that oral administration of 50 mg. of methantheline decreased gastric pepsin output to about 40 per cent of control, without significantly changing concentration. The reduction to 21 per cent of control observed in our experiments probably attests to the greater efficacy of intravenous administration in the dosage used. It should be noted that, because pepsin is determined after complete activation of pepsinogen and at a buffered pH of 4.9, the values obtained are independent of gastric acidity. In view of the fact that pepsin, as well as acid secretion, is increased in duodenal ulcer,[5] the suppression of pepsin secretion by anticholinergic drugs may be clinically useful.

Our measurements of uropepsinogen excretion were undertaken to study this suppressive effect over longer periods. The use of uropepsinogen levels as an index to gastric secretion, however, has several inherent difficulties. In the first place, because the environmental factors are not rigidly controlled, there is considerable day-to-day and week-to-week variation. This has also been the experience of Broh-Kahn, Podore and Mirsky,[6] who studied the variability of uropepsinogen excretion and whose data showed that it would not be unusual for values differing by 100 per cent from a subject's true mean to occur by chance. For this reason, multiple observations are required during any test period, particularly if relatively small changes are sought. Secondly, slowly developing shifts in baseline may occur, and may obscure changes resulting from the experimental procedure. Therefore, a control period after administration, as well as before, is essential. A third source of difficulty is the fact that some studies, notably those of Varro, Faredin and Novaszel,[7] cast doubt on the validity of the 1:99 distribution concept. It might be pointed out that, at a constant level of gastric secretion, a reduction in the gastric portion of the total pepsinogen output from 99 to 98 per cent might be associated with a 100 per cent increase in the urinary pepsinogen.

Nevertheless, the use of uropepsinogen secretion as a guide to the activity of antisecretory drugs has several important advantages. First of all, it reflects the influences of life stress on the subject's usual gastric secretory level. This means, for example, that in a

TABLE 3. *Effect of Propantheline on Urinary Pepsinogen Excretion.*

SUBJECT NO.	UROPEPSINOGEN				PERCENTAGE OF CONTROL ON PROPANTHELINE*	DAYS ON PROPANTHELINE
	1ST CONTROL PERIOD	PERIOD ON PROPANTHELINE	2D CONTROL PERIOD	CONTROL MEAN		
	units/hr.	units/hr.	units/hr.	units/hr.		
1	17.6	12.6	21.9	19.9	63	7
2	22.9	20.4	23.4	23.1	88	8
3	31.1	16.2	21.3	25.6	63	8
4	59.7	48.8	59.1	59.4	82	18
5	27.7	16.9	20.3	23.8	71	9
6	15.1	12.5	17.4	16.0	78	9
7	38.4	28.7	29.3	33.6	85	8
8	15.0	13.6	16.9	16.0	85	11

*Mean: 78 per cent.

patient with duodenal ulcer, it tests the ability of the drug to control gastric hyperactivity during the life situations that contribute to ulcer formation. This seems much more relevant than studies done wholly in the laboratory environment. Secondly, it offers the opportunity to study a drug over periods of weeks rather than hours, a matter of significance when drugs are intended for long-term treatment. Thirdly, the procedure of nocturnal collection of urine is less disturbing emotionally and requires less time for the subject than gastric intubation; specimens so collected have been shown by Mirsky et al.[8] to reflect alterations in life situations and to be free of significant deviation from values obtained by twenty-four-hour collections.

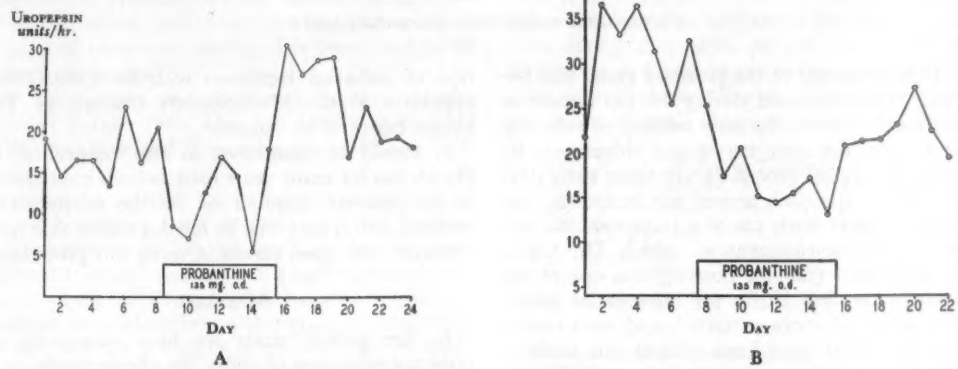


FIGURE 2. *Nocturnal Uropepsinogen Levels in F.S.* (A) *and H.S.* (B), *Subjects Receiving Propantheline. Note the different values in the control periods before and after medication.*

SUMMARY

In 10 subjects intravenous administration of methantheline caused a prompt fall in gastric pepsin production to an average of 21 per cent of basal values, without altering concentration significantly.

Oral administration of propantheline reduced nocturnal uropepsinogen excretion to an average of 78 per cent of control.

The possible usefulness of this control of pepsin secretion in the treatment of peptic ulcer is considered, and the practical and conceptual advantages of long-term studies of uropepsinogen excretion are presented.

We are indebted to Dr. Irwin Bross for assistance in statistical aspects of this study.

REFERENCES

1. Janowitz, H. D., and Hollander, F. Relation of uropepsinogen excretion to gastric pepsin secretion in man. *J. Appl. Physiol.* **4**: 53-56, 1951.
2. Gray, S. J., Ramsey, C., Reifenstein, R. W., and Benson, J. A. Significance of hormonal factors in pathogenesis of peptic ulcer. *Gastroenterology* **25**:156-172, 1953.
3. West, M., Ellis, F. W., and Scott, B. L. Simplified method for determining excretion rate of uropepsin. *J. Lab. & Clin. Med.* **39**: 159-162, 1952.
4. Whitrock, R. M., Hansen, R. W., Finch, R. L., and Chenoweth, M. B. Suppressing effect of Banthine on gastric and external pancreatic secretion in man. *Clin. Research Proc.* **1**:98, 1953.
5. Janowitz, H. D., and Hollander, F. Basal secretion of pepsin by human stomach. *J. Clin. Investigation* **31**:338-340, 1952.
6. Broh-Kahn, R. H., Podore, C. J., and Mirsky, I. A. Uropepsin excretion by healthy men. *J. Clin. Investigation* **27**:825-833, 1948.
7. Varro, V., Faredin, I., and Novaszel, F. Vergleichende Untersuchung des Pepsingehaltes des Magensaftes und der Menge des Uropepsins. *Klin. Wchnschr.* **30**:108-110, 1952.
8. Mirsky, I. A., Kaplan, S., and Broh-Kahn, R. H. Pepsinogen excretion (uropepsin) as index of influence of various life situations on gastric secretion. *A. Research Nerv. & Ment. Dis., Proc.* **29**: 628-646, 1950.

PRESENT-DAY TREATMENT OF PITUITARY ADENOMAS*

Surgery versus X-Ray Therapy

GILBERT HORRAX, M.D.,† MAGNUS I. SMEDAL, M.D.,‡ JOHN G. TRUMP, D.Sc.,§ RICHARD C. GRANKE, B.S.,¶ AND K. A. WRIGHT, B.A., B.S.¶

BOSTON AND CAMBRIDGE, MASSACHUSETTS

WHEN adenomas of the pituitary gland first began to be diagnosed during the last decade of the nineteenth century the only method of relieving the pressure on the optic nerves and chiasm was by some type of surgical procedure. In those early days the intracranial approach proved too hazardous, and most surgeons soon made use of a transphenoidal operation in the development of which Dr. Oscar Hirsch, of Vienna (now of Boston), was one of the pioneers. In the late 1920's the intracranial procedure became much more perfected, and most neurosurgeons since that time have utilized this method, believing that in the majority of cases, and particularly in those in which a large intracranial extension of tumor existed, a more radical removal of the adenoma could be accomplished and therefore more permanent results could be obtained. It is true that with these extensive intracranial expansions a greater hazard and higher mortality were inevitable, but it was only by such heroic measures that some patients could be saved from blindness or profound mental difficulties. Meanwhile, the mortality rate for the ordinary adenomas without great intracranial extension remained just as low as that with the transphenoidal operation — namely, 2 to 5 per cent.

By 1920 it was becoming apparent that radiation therapy had a beneficial effect upon some pituitary adenomas. At first it was used as an adjunct to operative removal of the tumor, and in some instances it was employed in the treatment of recurrent adenomas. By 1925 it was recognized that patients with pituitary adenomas should be given a trial of x-ray therapy before operation was advised, provided vision was not seriously affected. However, preoperative treatment by radiation did not become generally utilized until about the middle of the 1930's, and for many years thereafter most neurosurgeons believed from their experience that such treatment was effective in only a small minority of patients — very possibly because the treatment had been inadequate and had not been persisted in sufficiently. In general, this was the attitude of the Department of Neurosurgery at the Lahey Clinic until 1950, when the rotational type of radiation treatment with the 2,000,000-volt apparatus at the Massachusetts Institute of Technology began to be utilized.

It should be mentioned in this connection that Hirsch has for many years used radium implantations in his patients operated on by the transphenoidal method, and it may well be for this reason that he has obtained such good results in using this procedure.

MATERIAL

In the present study we have considered only pituitary adenomas of either the chromophobe or the chromophile (acromegalic) type, and have not included the so-called basophilic adenomas. Neither have we dealt with other tumors in the vicinity of the sella turcica and chiasm such as craniopharyngiomas, meningiomas, cholesteatomas and other rare lesions.

The material and statistics given in this paper represent a careful survey of all the adenomas of the two types in our personal series at the Lahey Clinic. The great majority of patients have been seen and examined at intervals since the time of their operation or radiation therapy, but with those living at a distance it has been necessary to learn about their condition from correspondence.

From November 1, 1932, through December 31, 1953, 303 patients were admitted to the Lahey Clinic with the diagnosis of either a chromophobe or a chromophile pituitary adenoma. In 143 patients this diagnosis was verified histologically by material removed at operation. In the other 160 the diagnosis was based on the demonstration of a large sella turcica by roentgenography, combined with other defects in the visual fields, optic-nerve pallor or outspoken evidence of pituitary disturbance. Of the total 303 patients adenomas of the chromophobe type were diagnosed in 243, and the other 60 gave acromegalic evidence of being due to a presumed chromophile adenoma. Some of these tumors may have been of the mixed type, but we have divided them in the way mentioned to simplify the classification (Table 1).

Our chief interest in this communication has been to compare the results obtained by either operation or radiation or a combination of the two, in a series of patients who were seen and treated by a single group of people whose methods have been the same throughout, either in the manner of operating or in that of giving the radiation therapy. For this reason only our own results have been tabulated with no attempt to compare them with the reports of others

*Presented at the annual meeting of the New England Surgical Society, Bretton Woods, New Hampshire, October 8, 1954.

From the departments of Neurosurgery and Radiology, Lahey Clinic, and the High Voltage Research Laboratory, Massachusetts Institute of Technology.

†Chief, Neurosurgical Service, Lahey Clinic; neurosurgeon, New England Deaconess and New England Baptist hospitals.

‡Chief, Department of Radiology, Lahey Clinic; chief, Department of Radiology, New England Baptist Hospital.

§Professor of electrical engineering, Massachusetts Institute of Technology.

¶Member, D. I. C. Staff, High Voltage Research Laboratory, Massachusetts Institute of Technology.

who may have utilized other methods or classified their results in a different manner.

Furthermore, we have been specifically interested in comparing the results of treatment during two periods, the first being that before our use of the 2,000,000-volt apparatus at the Massachusetts Institute of Technology and the second that during which this type of rotational therapy has been used in all pituitary adenomas.

For this purpose we have divided the patients into two main groups: those seen and treated from 1932 to 1949 inclusive and those seen from 1950 to 1953 inclusive.

It should be noted at this point that in speaking of relief or benefit to these patients we refer to their visual apparatus so far as operation versus x-ray treatment is concerned, since it is almost entirely because of visual failure that operations on the pituitary adenomas are undertaken, although x-ray treatment may be given for a variety of reasons such as headaches and various endocrine disturbances. In acromegalic patients especially, headache may be a feature of almost equal importance to visual loss, and in these patients it is also essential to arrest growth features if the adenoma is in an active stage; therefore, in patients with chromophile adenomas relief of these features is considered comparable to that of visual loss, which, indeed, may also be present.

Results

In the period 1932 to 1949 inclusive a total of 125 patients were treated by surgery only or surgery combined with radiation. Of this number, 108 survived the primary operations, and 79, or 73.1 per cent, were improved for periods varying up to eighteen years. Furthermore, it is known that 66 patients (61.1 per cent) maintained improvement for five to eighteen years, with several unheard from, so that this figure may be somewhat low.

Table 1. *Pituitary Adenomas, 1932-1953, Inclusive.*

Method of Diagnosis	No. of Cases
Chromophobe:	
Verified by operation	125
Verified by x-ray study etc.	118
Total	243
Chromophile:	
Verified by operation	18
Verified by x-ray study etc.	42
Total	60
Grand total (both types)	303

In this same period 173 patients were treated by radiation only or were operated on because they had received no benefit from radiation. However, of this total number 74 patients showed no visual loss or other serious symptoms such as intractable headaches in acromegaly. Therefore, 99 patients were treated for visual loss, or for severe headache and progressing acromegaly. Of this number 58, or 58.5 per cent, had to be operated on because radiation therapy with the usual type of apparatus was not effective (Table 2).

A word should be said about the type of radiation given during this earlier period. A total of 1800 to 2400 r was delivered to the tumor through two temporal portals in most cases. The patient was then checked at intervals of one or more weeks, depending on circumstances, with particular reference to visual fields and acuity. If vision was not improved or had not deteriorated seriously after two or three months, a similar series of radiation treatments might be given. In some cases a third or fourth series was used. However, if vision deteriorated or was not held at a useful level within three to six months, operation was advised. It is possible, in view of present knowledge, that we should have waited longer in some patients, but this has always been a most difficult question to decide.

Table 2. *Results of X-Ray Treatment (1932-1949 Inclusive) of Chromophobe and Chromophile Adenomas.*

Treatment	No. of Cases
X-ray treatment only or surgery because treatment not effective	173
(Less patients without visual loss	74)
	99
Operation because x-ray treatment not effective	58(58.5%)

In the recent four-year period, 1950 to 1953 inclusive, a total of 63 patients of both types were seen and treated. Ten of these were operated on without having had radiation under our supervision although 2 patients had been operated on elsewhere and had received radiation therapy without benefit. Likewise, 2 patients in the group were operated on purely to control spontaneous cerebrospinal-fluid rhinorrhea. There were therefore 8 patients in whom vision was so poor (usually 20/200 or less) that operation was considered imperative before a trial of radiation. One of the 10 patients died postoperatively, but the others have not been followed long enough for us to tell what their eventual outcome will be. So far their progress has been satisfactory.

The most significant data in this recent period come from the review of the patients who received radiation therapy with the 2,000,000-volt apparatus at the Massachusetts Institute of Technology. There were 53 patients in this group, all of whom received a tumor dose of 4000 r by the rotational method. Fifteen of these patients were treated for glandular difficulties only and showed no visual loss or other serious symptoms, leaving 38 patients who had failing vision for which treatment was indicated. At varying intervals after treatment it was considered

necessary to operate on 7 patients because vision did not improve, this number representing 18.4 per cent of the 38 patients with visual loss. A comparison of this figure with the 58.5 per cent of patients who had to be operated on in the period before rotational therapy shows the tremendous gain afforded by this method of treatment (Table 3). One other patient

TABLE 3. *Results of X-Ray Treatment (1950-1953 Inclusive) of Chromophobe and Chromophile Adenomas.*

TREATMENT	NO. OF CASES
X-ray treatment only or surgery because treatment not effective	53
(Less patients without visual loss	15)
	38
Operation because x-ray treatment not effective	7(18.4%)

was operated on in the last four years for a cerebrospinal-fluid rhinorrhea.

Furthermore, on a review of the records of the patients who were operated on it was obvious that in 2 there was no pressure on the optic nerves or chiasm from the adenoma when the area was exposed and therefore that operation had accomplished nothing; 1 of these patients eventually recovered normal vision. Thus, there were only 5 patients out of the 38, or 13.1 per cent, who had conditions for which operation was necessary after the courses of rotational therapy.

Although the length of time since the treatment only runs up to four years, 30 of the 38 patients with visual loss or serious symptoms of other kinds have shown excellent improvement for eight months to four years, with 4 patients stationary and 4 others either too recent or unheard from.

DISCUSSION

From what has been said, we have not meant to imply that the rotational type of therapy with the 2,000,000-volt apparatus is the only method by which patients with the lesion in question can be treated adequately. It is perfectly possible to deliver 4000 r to the tumor by the usual 200 K. V. machine, but large areas of permanent depilation would result and this is a considerable factor with many patients. Furthermore, there would doubtless be an intense radiation reaction in the skin.

However, on review of the present material, it seems almost certain that we should have given considerably larger amounts of radiation to the patients we treated before we had the use of the 2,000,000-volt apparatus even though they might have been subjected to permanent hair loss, since our present-day better results are apparently due to this larger dosage.

SUMMARY

The necessity of surgical interference in the treatment of pituitary tumors after a preliminary trial of radiation therapy has been investigated. It was found that, in our experience, before the use of rotational therapy with the 2,000,000-volt apparatus, 58.5 per cent of patients required operative removal of the adenomas. This may well have been due to the fact that they did not receive an adequate radiation dosage. Since receiving 4000 r by the rotational method, only 18.4 per cent of patients have had to be operated on, and even this figure may be somewhat high.

MEDICAL PROGRESS

COAGULATION, HEMORRHAGE AND THROMBOSIS (Concluded)*

BENJAMIN ALEXANDER, M.D.†

BOSTON

Clinical Considerations

The physician is thoroughly aware that prothrombinopenia causes retarded thrombin formation (elevated prothrombin time), which can result in hemorrhagic phenomena. Likewise, deficiency of accelerator globulin or of serum prothrombin conversion accelerator causes hemostatic disability. More significantly, the clinical manifestations of all these disorders are practically identical. This is not surprising since each leads to inadequate thrombin elaboration. Details may be obtained from certain exhaustive clinicolaboratory studies.[43,44,144]

This newer knowledge permits reclassification (Table 3) of the general hypoprothrombinemias into two major groups — *true* hypoprothrombinemia and *pseudo*hypoprothrombinemia. The cardinal laboratory abnormality common to all, and serving to distinguish these cases from most of the other hemorrhagic disorders, is an elevated one-stage prothrombin time.

*From the Medical Research Department of the Yamins Research Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

The work from the author's laboratory described in this report was supported in part by a research grant, H-656, from the National Heart Institute of the National Institutes of Health, Public Health Service, and in part by the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-171.

†Associate professor of medicine, Harvard Medical School; associate director, Medical Service, Beth Israel Hospital.

TABLE 3. *Classification of Hemorrhagic Diseases.*

I. Defective coagulation — derangements in plasma constituents:

A. First phase — deficient thromboplastin formation:
1. Hemophilia:
a) Deficiency of antihemophilic factor
b) Deficiency of plasma thromboplastic component
2. Deficiency of plasma thromboplastin antecedent
3. Hemophilioid disease — acquired
4. Circulating anticoagulants — lupus erythematosus; hyperglobulinemia; multiple myeloma; anaphylactic shock; ?radiation injury; ?leukemia.

B. Second phase — deficient thrombin formation:
1. True hypoprothrombinemia:
a) Congenital — ?familial
b) Acquired:
i. Idiopathic
ii. Liver disease
iii. Vitamin K_1 deficiency — neonatal type: sprue; biliary & other gastrointestinal diseases.
iiii. Prothrombinopenic drugs — Dicumarol; Tromexan; phenylindanedione; compound 63; Warfarin; coumarin; Hedulin; etc.
2. Pseudohypoprothrombinemias:
a) Deficiency of accelerator globulin (parahemophilia):
i. Congenital — hereditary
ii. Acquired — liver disease; purpura fulminans; ?acute leukemia.
b) Deficiency of serum prothrombin conversion accelerator (hypoproconvertinemia):
i. Congenital — hereditary
ii. Acquired — liver disease; prothrombinopenic drugs; neonatal type.

C. Third phase — defective fibrin formation:
1. Hypofibrinogenemia:
a) Congenital — hereditary
b) Acquired — liver disease; bone-marrow disease; pregnancy; neoplasia of prostate, stomach etc.; pulmonary manipulation; excessive fibrinolytic activity.

II. Defective coagulation *plus* vascular abnormalities:

A. Thrombocytopenic purpura:
1. Idiopathic — Werlhof's disease
2. Secondary
a) Bone-marrow disease
i. Cancer — leukemia; lymphoma; myeloma; metastatic disease.
ii. Aplastic anemia — idiopathic; chemical or physical agents.
iii. Other marrow disorders — pernicious anemia; osteomyelofibrosis; myelophthisic involvement due to xanthomatoses, reticuloses; miliary tuberculosis.
iiii. Splenic & hepatic disorders — "hypersplenism"; Banti's and Felty's syndromes; hemolytic icterus; hepatic cirrhosis.
iiiii. Other diseases:
a) Infections — septicemias such as meningococcemia & bacterial endocarditis; typhus; typhoid fever; infectious mononucleosis; influenza; measles; scarlet fever; diphtheria; others.
b) Nephritis; lupus erythematosus; thrombotic thrombocytopenic purpura.
c) Allergy — foods, chemicals and drugs — gold; bismuth; barbiturates; antiepileptic drugs; iodides; ergot; hair dyes; others.

B. Thrombasthenia (thrombopathia — Willebrandt's disease) — pseudohemophilia; qualitative platelet abnormality plus deficiency of antihemophilic factor.

III. Vascular abnormalities:

A. Vitamin C and ?vitamin P deficiency

B. Hereditary hemorrhagic telangiectasis (Rhendu–Weber–Osler disease)

C. "Vascular purpura" — hypertension; arteriosclerosis; diabetes mellitus; polycythemia vera; infections; renal disease.

D. "Anaphylactoid" purpura
1. Henoch & Schönlein types; Osler erythemas.
2. Allergic purpura — infectious (same as above in II, 2, a, iiiii, a); chemicals (many same as above in II, 2, a, iiiii, c).

Obviously, all cases of congenital hypoprothrombinemia previously reported must now be rescrutinized[148] since it is likely that in some the defect was actually deficiency of accelerator globulin or conversion accelerator rather than of prothrombin itself. That congenital hypoprothrombinemia occurs, however, cannot be doubted, although it is exceedingly rare.[162,163] Study of such unique cases has provided information of academic as well as practical value, obtained under conditions that could not be duplicated experimentally.

Certain quantitative relations deserve emphasis. Regarding plasma prothrombin, 10 per cent of normal (by methods described in the first section of this review[13,15]) is the approximate critical level below which bleeding is likely to ensue. Moreover, from fragmentary evidence it appears that man consumes his prothrombin daily.[162] To regenerate it, a healthy liver is necessary.*

It is now apparent why, in the hypoprothrombinemias, the clotting time in glass is normal more often than not, in contrast to disorders concerned with defective thromboplastin formation. One unit (Iowa) of prothrombin yields sufficient thrombin to clot plasma in approximately *twenty seconds.* Normal plasma contains 300 to 400 units of prothrombin per cubic centimeter. Obviously, all that is required to clot blood in a normal interval *(ten to fifteen minutes)* is an amount of thrombin obtained from much less than 1 per cent of its prothrombin. For longer clotting times even less thrombin is needed. It would be rarely, indeed, that such degrees of prothrombinopenia would be encountered. These considerations, moreover, bring out strikingly the limited diagnostic value of clotting-time determinations. When prolonged, they obviously indicate a profound clotting abnormality. The physician must always remember, however, that a normal clotting time does not exclude many equally serious clotting defects.

The quantitative relations between the prothrombin time and levels of accelerator globulin or proconvertin are similar to those with prothrombin. Thrombin formation becomes progressively retarded and curtailed as their respective concentrations decrease (Fig. 5, 9 and 10), hemostasis becoming more and more compromised when they descend below 10 per cent of normal. The abnormality is readily rectified by transfusion[43,44] (Fig. 11). Because multiple defects are not infrequent with these factors as well as with platelets and fibrinogen, particularly in *liver disorders,*[10,164-168] the more than additive untoward effect of multiple abnormalities deserves re-emphasis, as discussed in the first section of this review.

Knowledge of these quantitative relations permits accurate appraisal of replacement needs by transfu-

*This is not the same as saying that prothrombin is *made in* the liver. I have never been able to find prothrombin in fresh aqueous or saline liver extracts by a method capable of detecting less than 0.1 per cent in plasma. The generally accepted view that the liver is the exclusive source of prothrombin has also been recently challenged by more direct experimental evidence.[101]

sion. Normal coagulation can almost be assured when adequate amounts of the factors are replenished and maintained. Requirements can readily be computed from an estimate of the circulating plasma volume and from the content of the particular clotting factor in both the patient's blood and material to be infused. It must be remembered that, because of the pronounced lability of accelerator globulin, bank blood or plasma is apt to be low in this factor. Also, most lyophilized plasma is devoid of it. Thus, when substantial blood replacement is necessary, as in extensive

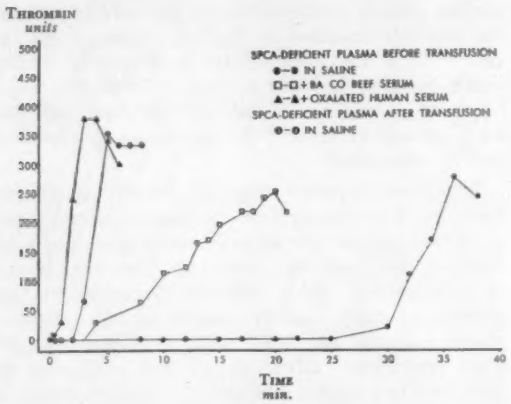


FIGURE 11. *Prothrombin Conversion in Deficiency of Serum Prothrombin Conversion Accelerator (SPCA) before and after Transfusion, Showing the Effect of in Vitro Addition of Normal Serum, or of in Vivo Transfusion, on the Retarded Two-Stage[17] Prothrombin Conversion in Plasma Congenitally Deficient in Conversion Accelerator.*

Abscissa represents incubation time (room temperature) of a mixture comprising patient's oxalated plasma, human brain thromboplastin and calcium combined with saline solution, barium carbonate adsorbed bovine serum or oxalated normal human serum. The patient's prothrombin was normal. The bovine serum still contained 2 per cent residual conversion accelerator, unremoved by the barium carbonate. (Note the rapid and complete prothrombin conversion after transfusion with normal blood or after the in vitro addition of normal serum devoid of both prothrombin and accelerator globulin; human brain thromboplastin was used throughout.)

surgical procedures or as a consequence of massive bleeding from any cause, the bank materials, although obviously valuable, should not be used exclusively. Moreover, in hemorrhagic shock, prothrombin, prothrombin conversion factors and fibrinogen levels may drop significantly owing to depletion and fibrinolytic mechanisms, and probably also because of liver anoxia adversely affecting their regeneration.[169-171]* Under such circumstances, a shift from *bank* to *fresh* blood or plasma has in my experience proved life saving in some cases, presumably by breaking a vicious circle in which bleeding persists because the original hemorrhage and its treatment with defective blood induces a hemorrhagic diathesis that fosters further hemorrhage.

*It is therefore important to bear in mind that hypoprothrombinemia may be a *consequence* of massive bleeding as well as a *cause*.

Hemorrhagic disease of the newborn. Although the exact pathogenesis of this disorder is still debatable, the physiologic clotting abnormality in the immediate neonatal period, which has recently been clarified, is probably significant. At least two deficits exist or develop within the first few days†: a low prothrombin and, perhaps even more significant, a low serum prothrombin conversion accelerator.[172-174] I have encountered conversion-accelerator values in 2 infants of less than 1 per cent of normal within forty-eight hours of birth.‡ The prothrombin was 30 per cent of normal in 1 subject and less than 1 per cent in the other. Both had severe hemorrhagic manifestations, which, together with the conversion accelerator and prothrombin, responded rapidly (within hours) to vitamin K_1.§

It is likely that these physiologic defects, when aggravated by difficult and long labor, anoxia and shock, with consequent liver embarrassment and negligible intestinal biosynthesis of vitamin K_1 in the infant, play an important part in melena neonatorum.

THROMBIN ANTITHROMBIN

Basic Aspects

Not considered in the classic scheme but of great importance in the over-all clotting mechanism is antithrombic activity (Fig. 1). The ability of plasma to inactivate or otherwise to dispose of relatively large amounts of thrombin¶ is largely referable to a plasma protein frequently called "natural antithrombin."[34,175,176] Antithrombic activity has also been attributed to fibrinogen fibrin, with little question that during fibrin deposition a significant amount of the thrombin is rapidly adsorbed by the clot, from which it later is slowly released.[177]

Indeed, some investigators consider fibrin to be the important physiologic antithrombin.[178]

The antithrombic activity of heparin is also well known, but its precise method of action is still obscure. From recent studies[59] it appears that the anticoagulant functions mainly via a cofactor in plasma[176] that differs from "natural" antithrombin and from fibrinogen. There is some evidence, however, that heparin also adversely influences the thrombin-fibrinogen interaction.[34]

Regardless of the exact explanation for antithrombic activity, the entire mechanism clearly permits neutralization of thrombin released in the blood, in this way competing with the fibrinogen for the thrombin as it evolves. In this respect, antithrombin can be considered a true inhibitor of clotting.

†This may be viewed teleologically as a means of assuring relative blood hypocoagulability to protect against thromboembolism, which might arise from the relative inactivity of the fetus, from anoxia of labor and from the hemolytic sequence associated with the shift from intrauterine to extrauterine life.

‡In 1 case the maternal conversion accelerator was, if anything, higher than normal. In the other, maternal clotting factors were normal. Elevation of conversion accelerator in pregnancy and its possible significance are elaborated on below in the discussion of thrombosis.

§Here, as in other prothrombinopenic and accelerator-deficient states, the natural vitamin seems far superior to the water-soluble derivatives.

¶Approximately 800 to 1000 units per cubic centimeter.

Clinical Considerations

Despite repeated attempts to establish excessive antithrombic activity as the underlying cause of disturbed hemostasis, I know of no well studied, documented case. Similarly, and conversely, I know of no case in which antithrombic inadequacy has been conclusively shown to be the basis for thrombotic disease. Nevertheless, antithrombin abnormalities have recently been reported in several pathologic conditions, and may therefore have far-reaching clinical significance.

Antithrombic activity is said to be significantly reduced in fibrocystic disease of the pancreas,[179] in severe parenchymatous liver disease or malignant metastatic involvement of that organ[180] and in endangiitis obliterans.[181] Conversely, it is reported to be high in acute pancreatitis[182] and carcinoma of the pancreas with biliary obstruction.[183] Accordingly, antithrombin determinations appear promising in the differential diagnosis of disorders of the liver, pancreas and biliary tract.

Fibrinogen Fibrin

Notable advances have occurred in this area of coagulation. These have included purification, and elucidation of the properties, of fibrinogen and fibrin,[184-186] study of the kinetics of the thrombin fibrinogen interaction[187-190] and demonstration of its enzymatic (proteolytic) nature.[191-195] Also reported are clinicolaboratory studies on afibrinogenemia, both congenital and acquired.

Congenital Afibrinogenemia

Relatively few cases (approximately 18) of this rare hemorrhagic disorder have thus far been documented.[59,60,196] Occurring as a heredocongenital defect, with a greater propensity among consanguineous marriages, such cases have provided unique investigational opportunities that have yielded fundamental knowledge not otherwise obtainable. From such studies it may be concluded that the critical level of fibrinogen required for normal coagulation is approximately 100 mg. per 100 cc., that the half life of fibrinogen in the circulation is about a day and that, contrary to earlier concepts, the following coagulation reactions are independent of the fibrinogen-fibrin conversion mechanism: platelet agglutination, prothrombin consumption, accelerator-globulin activation and plasma antithrombin activity. It is now known that afibrinogenemic blood that is incoagulable will nevertheless rapidly undergo sequential changes — termed "chemical coagulation" — when exposed to a foreign surface. Knowledge of such changes, and of how they can be prevented, is important in effective blood banking and plasma processing.

Acquired Afibrinogenemia

More frequently encountered are cases of *acquired* afibrinogen — or hypofibrinogenemia. That it occurs in liver disease has long been known, but only recently have internists, surgeons and obstetricians become alerted to this dread complication of shock,[169,171] of pregnancy,[197-199] of pulmonary manipulation[200-202] and of neoplastic disease involving the pancreas, prostate or stomach.[35,203] The precise mechanisms whereby fibrinogen-fibrin deficiency arises in many of these conditions is obscure. In some cases excessive fibrinolytic activity has been demonstrated in the plasma, the activated plasminogen-plasmin system* readily destroying fibrin as well as fibrinogen (more slowly). According to Tagnon,[35] anoxemia appears to be the common denominator of many conditions associated with excessive fibrinolytic activity. In pregnancy either or both of two mechanisms have been postulated: an in vivo "defibrination," caused by liberation into the circulation of thromboplastic elements from amniotic fluid, decidua or placental fragments[198]; and activation of plasminogen by tissue "fibrinolysokinase" from these tissue elements.[204]

Regardless of the cause, disturbed clotting becomes evident, first in a *prolonged* one-stage whole-plasma prothrombin time as plasma fibrinogen progressively falls below 100 mg. per 100 cc. Conversely, a *normal* prothrombin time excludes clinically significant fibrinogen deficiency as a cause of bleeding. Also, if excessive fibrinolysis is present, the clot will be observed to lyse rapidly. This may be extreme (within less than an hour) when fibrinolysis is marked. Fibrinolysis is clinically significant if the clot disappears in less than twenty-four hours at 37°C.[35] provided that the original fibrinogen concentration is sufficient to form a normal clot. In severe hypofibrinogenemia alone, however, lysis may seem rapid simply because the thin, fragile clot will quickly retract to a small and occasionally invisible nub.

It is also noteworthy that, with excessive fibrinolysis, additional defects are frequent, such as mild to moderate thrombocytopenia, hypoprothrombinemia and deficiency of accelerator globulin.

Effective management requires prompt detection and correction. As mentioned above, blood incoagulability (in complete deficiency), careful observation of whatever clot may form and the one-stage prothrombin time on the whole plasma, aside from actual fibrinogen determination, will help ascertain whether a critical deficiency exists. Therapy should consist of fibrinogen replacement by intravenously administered fraction I, readily obtainable from local Red Cross sources. A minimum of about 5 gm. is necessary (contained in each ampoule of Red Cross purified fibrinogen). This may need to be repeated frequently as indicated by the fibrinogen level, which will be influenced by several other therapeutically amenable variables such as anoxia, persistent bleeding and shock, and poor liver function. Obviously, correction of the underlying disorder (neoplastic disease or com-

*Because of limitation in space a review of progress on the fibrinolytic mechanism in plasma must be omitted despite its close relation to coagulation. This subject is well covered in recent excellent reports and discussions.[201,204-207]

plication of pregnancy) is also indicated whenever possible.

Differential Diagnosis of the Hemorrhagic Disorders

Reclassification of the hemorrhagic diseases is now opportune in the light of more extensive knowledge (Table 3). With this in mind, one may consider the differential diagnosis and general approach to patients who present suggestive or overt evidence of a hemorrhagic diathesis. Together with the classification, Table 1 may help one understand the clinically significant coagulation components, their properties and function, the disorders respectively associated with their abnormality, some points of differential diagnosis and the important therapeutic approaches.

The history is of commanding importance in establishing whether bleeding has its pathogenesis on a local basis (ulcer, neoplasm, infection and so forth) or whether it is caused by a generalized hemostatic failure. It is quite rare for a patient to have a serious bleeding disorder without giving a significant history of hemorrhagic phenomena occurring spontaneously or after trauma, and involving skin, mucous membranes, muscles or joints. One minute of simple questioning can frequently save the surgeon, otolaryngologist and obstetrician many a trying and avoidable experience.

Once having established the likelihood of a hemorrhagic diathesis, the physician will seek to learn whether it is due to a coagulation defect or a vascular disorder, or both. This purpose is best accomplished by recourse to a few informedly selected, yet simple procedures comprising the capillary fragility test; the routine blood examination, of which the stained film is the most important; the bleeding time; the clotting time*; inspection of the clot for retraction and lysis; the one-stage plasma prothrombin time; and the prothrombin consumption test. If all the results are normal, it is most unlikely that a coagulation defect underlies the hemorrhagic phenomena. Some vascular disturbance then becomes suspect.

In most cases a skilled glance at a good blood film will determine thrombocytopenic purpura, especially when it is considered in conjunction with the type of bleeding manifestations, the tourniquet test and the bleeding time. For determination of the clotting time, the capillary tube method is considered valueless. The Lee–White procedure, meticulously performed, is the only reliable method. The vein must be entered by "primary intention,"† — that is, with the first stab, — and the range of normal values must be known for the particular batch of test tubes employed.[13] Here, as with all these tests, the old Turkish proverb is particularly pertinent: "Never descend into the well with a rotten rope." Poor technic can be dangerously misleading.

A prolonged clotting time immediately indicates retarded coagulation, but, as already mentioned, several types of defect may hide behind a normal clotting time. The prothrombin determination and the prothrombin consumption test are invaluable. A normal plasma prothrombin time practically excludes deficiency of prothrombin, accelerator globulin, serum prothrombin conversion accelerator and fibrinogen as being pathogenetically significant. If, in addition, the residual serum prothrombin is elevated (indicating a poor prothrombin consumption) the conclusion may be drawn that the defect lies in the first phase of clotting — that is, thromboplastin generation. To establish the precise defect more complicated tests must be used (measurement of antihemophilic factor, plasma thromboplastic component and antecedent, tests of platelet function, antithromboplastins and so forth). Therapeutic management depends almost entirely on transfusions with blood or plasma in combination with the use of thrombin applied locally to bleeding areas that are readily accessible.

Defects of the second phase of clotting are readily disclosed by a prolonged one-stage prothrombin time. But this throws no light on which factor, or combination of factors, is involved. For this, further tests are required. These are not yet available in most clinical laboratories. Regardless of the particular underlying defect, the physician is justified in prescribing vitamin K_1 and, when indicated by the degree of bleeding, blood or plasma. When deficiency of accelerator globulin is suspected the material should be fresh.

Diagnosis of third-phase disturbances (fibrinogen-fibrin abnormality) is easily made by the alert physician familiar with the few diseases in which they occur as complications — namely, pregnancy, pulmonary surgery, cancers of the prostate, stomach and pancreas. The one-stage prothrombin time will be prolonged, and this will be corrected if the system is supplemented with fibrinogen in one way or another. Treatment has already been described briefly.

Thrombosis As Viewed by a Coagulationist

"It requires a long-necked observer to view the whole firmament out of one window" (J. Arthur Thomson).

Outstanding advances in coagulation, long suspected of being of basic significance in the pathogenesis of intravascular coagulation,[208] have stimulated renewed study of thromboembolic disease. Little imagination is required for postulating that this disorder represents one side of the coagulation coin, the other being hemorrhage.‡ Yet, despite more extensive knowledge, there is still no reliable test for detecting the prethrombotic, incipiently thrombotic or actually thrombotic state,[210] not to mention a satisfying explanation of the etiology. Nevertheless, recently ac-

*This is so rarely abnormal in females that it can be routinely omitted in this sex unless indicated in more elaborate study.

†This is also true when blood is drawn for prothrombin determination.

‡How provocative is the paradox of both thrombotic and hemorrhagic tendencies coexisting in polycythemia vera, with no satisfactory explanation for either! The two abnormalities are also described in thrombotic thrombocytopenic purpura.[209]

quired information has spearheaded rational advances in the management, if not the prevention, of thromboembolism and has stimulated a direct experimental attack on the problem.

Pathogenesis

With due respect for the part possibly played by extracoagulation factors such as inactivity, blood stasis, vascular trauma, shock, anoxia and other pathologic states, present consideration is limited to the clotting process itself. As is evident in the earlier discussion, there is reason to believe that the chemical sequence termed "coagulation" proceeds continuously within the body, although very slowly. How else is one to explain the relatively rapid turnover of individual clotting constituents such as antihemophilic factor, plasma thromboplastic component, platelets, prothrombin, accelerator globulin, serum prothrombin conversion accelerator and fibrinogen? It is also reasonable to suppose that the resultant fibrin particles, of microscopic or macroscopic size, reach the lesser circulation and are then filtered out by the lungs, which thus serve another important role besides ventilation — namely, *blood filtration*. Whenever coagulation fails to be accelerated in time of need, hemorrhage looms; if it is unduly accelerated when uncalled for, thromboembolism threatens.

It appears a priori that thrombosis cannot occur when the blood is incoagulable. This *sine-qua-non* relation may not be as definite, however, as it seems at first glance. Platelet agglutination occurs even in incoagulable afibrinogenemic blood.[59] Indeed, formation of such conglomerates is the sole method of "thrombus" formation in certain invertebrates. It is well known,[211-213] furthermore, that one of the first changes visible in mammalian blood exposed to a foreign surface, such as a traumatized blood vessel, is the piling up of the platelets in aggregates and masses both within and outside the vessel. The terms "coagulability" and "incoagulability" must therefore be defined more specifically, with particular reference to the component or phase of coagulation implicated. This consideration is particularly pertinent to the rationale of anticoagulant drugs, their aim and their action. Obviously, agents inducing incoagulability by defibrination, for example, might be far less effective against thrombosis than agents blocking platelet agglutination. Thus, complete understanding of the factors controlling platelet agglutination is of more than academic importance when viewed in the framework of the prevention and treatment of thromboembolic disease.

To focus more sharply on the problem, one might attempt to answer several questions. What new evidence supports the concept that deranged coagulation plays any role in thromboembolism? What phase, component or components of clotting may be implicated? What procedures or drugs can be invoked to prevent or control such aberrations? Are they effective?

Little would be gained by a detailed account of the almost innumerable claims and counterclaims regarding blood hypercoagulability in thromboembolic states,[214,215] ever since Virchow[208] originally postulated this as one of the three etiologic factors.* It is likely that much of the conflicting evidence and varying interpretations are referable to differences in technics of study, to failure to consider the limitations and inaccuracies inherent in the rough tests employed, to the subtleties and complex interrelation of the variables involved and so forth. One thing is certain, however; there is a close clinical association between intravascular thrombosis† and certain pathologic conditions.

With each improvement in analytical method, and with each disclosure of a new factor, interest becomes renewed in the possible role of disturbed clotting in thrombotic disease. The conversion-accelerator (convertin) system is currently receiving close attention. In one condition associated with a high rate of thromboembolism — namely, pregnancy — marked elevations of conversion accelerator are found. In a recent study in these laboratories,[140] women in various stages of pregnancy exhibited a mean average plasma proconvertin level of 189 per cent (range of 80 to 560), in striking contrast to 82 per cent (range of 60 to 147) for the nonpregnant group. In the great majority the values exceeded all those (except one) in the nonpregnant; in 10 cases they were threefold to fivefold higher than the nonpregnant average, and in 5 they were more than five times this value. Moreover, there was a suggestive correlation between the proconvertin level and the duration of pregnancy. Shortly after delivery the elevated values tended to return to normal: in 24 subjects the mean average concentration three to five days post partum was 114 per cent, in contrast to 150 per cent in the same cases shortly before delivery.

Prothrombin was less significantly altered. However, in 9 women it was 140 to 180 per cent of normal, compared with a mean average of 98 per cent (range of 58 to 128) in the controls.

These findings are in agreement with the results of similar studies from other laboratories.[172-174] This investigation continues in pregnancy, and is being extended to myocardial infarction and postsurgical states.

The results constitute direct evidence of an increase in a specific clotting constituent (other than fibrinogen) in a condition known for its high rate of thromboembolism. This lends credence to the con-

*The other two in the triad are: venous stasis[216] and injury to the vessel wall.[217-220] Much has been learned of the former, particularly the effect of bed rest and ambulation.[218] Regarding vascular damage, recent work suggests the importance of small physiologic changes in electrostatic force resulting from extremely mild trauma. This is said to be sufficient to induce local thrombosis.[60]

†It should also be pointed out that "thrombosis" is not synonymous with "thromboembolism." The dissociation between these two in polycythemia vera is of interest. Despite the extraordinarily high prevalence of thrombosis in this disease, embolism, in my experience, is extremely rare. Perhaps the clots that do form in polycythemia are firmer, and anchored more securely.

cept of hypercoagulable blood in pregnancy.* Additional support is provided in the demonstration of increased platelet adhesiveness in the early post-partum period.[221,222] Thus, with the venous stasis known to exist in late pregnancy, there may be a delicate state of equilibrium readily vulnerable to liberation of thromboplastic material into the circulation from the gravid uterus under certain circumstances.[198]

The known properties of proconvertin — its rapid activation by thromboplastin and its interaction with platelets yielding an important prothrombin conversion factor[54,223] — afford a working concept of the pathogenesis of thromboembolism centered in the conversion-accelerator mechanism in conjunction with venous stasis. Consistent with this theory is the experimental production of *local* thrombi by the *systemic* intravenous infusion of serum or purified accelerator fractions.[224] Clots can be laid down at will anywhere in the veins or arteries by infusion of accelerator-rich material at a site far removed, followed promptly by partial or complete local obstruction of blood flow at any point where the clot is desired. No other untoward effects are observed. Thus, there is direct evidence that a coagulation factor (not thrombin) that is an intermediary product of the clotting process itself (discussed in the second section of this review as "autocatalytic factors in coagulation") can induce intravascular coagulation under certain conditions. This exciting work has also provided an extremely useful and reproducible method for studying the pathophysiology of thrombosis, embolism and their attendant phenomena.

Therapeutic Considerations

Anticoagulants. Difficulty in diagnosis presents an enormous stumbling block to management of thromboembolism. There is no test that will reliably indicate whether a given person has had, is having or will have thrombosis. Diagnosis rests solely on clinical criteria, which in my experience have proved most unsatisfactory. Moreover, there are many who believe that the most dangerous thrombotic process is the silent type with minimal symptoms and signs. Distinction has been made between "phlebothrombosis," pertaining to this type of clot, and "thrombophlebitis," referring to thrombi exhibiting more prominent clinical as well as pathological findings. It is not surprising, therefore, that anticoagulant therapy is advocated and widely used by many on a routine basis in certain clinical states associated with a high rate of thrombosis, as well as in specific overt cases. Under such circumstances, the evaluation of results must depend on extensive statistical study — for example, the recent surveys of anticoagulant therapy in myocardial infarction[225,226] and in congestive heart failure.[227,228] Controversy still rages concerning indications for its use and its effectiveness here, not to mention other conditions.[229-231]

*Here, again, one is tempted to interpret this teleologically as a mechanism designed to assure prompt hemostasis after parturition.

It is not known, moreover, whether pathogenetic mechanisms are the same in all thromboembolic states. Conceivably, intravascular clotting complicating myocardial infarction may arise from a coagulation disturbance quite different from that complicating surgery or pregnancy. One might accordingly select different anticoagulants for these conditions, aimed at different phases of the coagulation sequence, assuming that such interference was both effective and safe. Some evidence is already available that heparin is more effective than Dicumarol in blocking accelerator-induced experimental thrombi.[232] The reverse may be true in other situations.

There can no longer be any question that, under experimental conditions, intravascular coagulation can be blocked or hindered by anticoagulants. Thus, the rationale for their therapeutic use is sound. Moreover, experience has amply indicated that they can be given safely, although the physician must be exceedingly cautious when prescribing them in view of the homeostatic importance of clotting. Lastly, most statistical data support the view that anticoagulants are clinically effective in the prevention and treatment of thromboembolic disease. Accordingly, when this disorder is anticipated or suspected, the physician cannot afford to withhold such therapy, however much he may be impelled by conflicting claims to await more conclusive support. In my view the limited state of present knowledge does not justify such inaction.

Prothrombinopenic drugs (Dicumarol, Tromexan, phenylindanedione, compound 63, Hedulin, Coumadin and so forth). Drug-induced hypoprothrombinemia is probably the most common clotting defect observed. This statement helps define the scope and importance of the problem. It is noteworthy that I have already encountered several cases of hypoprothrombinemia factitia.

Since the discovery of Dicumarol many related compounds have been synthesized in search of an agent that would permit simpler and less hazardous control of prothrombic activity. Claims for their respective virtues have frequently been supported only by scanty and uncritically evaluated evidence. All these compounds act by reducing at least two components: prothrombin and proconvertin. Some investigators believe that the effect is preponderantly on proconvertin,[233,234] and most recent evidence suggests that yet another factor may be involved.[235]

Although space limitations preclude detailed consideration of the use of these drugs in myocardial infarction, congestive heart failure, postoperative states and other conditions, certain points deserve emphasis. In my opinion one agent offers little advantage over another. The claim that Dicumarol acts more slowly than certain other derivatives is contrary to the evidence: within twenty-four hours Dicumarol induces a profound decrease (80 per cent or more) in plasma prothrombic activity.[15] Even with a much more solu-

ble prothrombinopenic drug given intravenously[236,237] this prothrombinopenia is not obtained at a significantly faster rate.

Much of the controversy and numerous difficulties, some apparent and others real, regarding control of the induced clotting defect can be attributed to different and frequently faulty assay procedures; to variation in drug dose and absorption; to shock or other pathologic processes affecting prothrombin regeneration; to the speed with which prothrombin and serum prothrombin conversion accelerator are normally consumed and replenished within the body; and to the action and metabolism of the drug itself. As with all anticoagulants, there is no simple rule or formula that can replace thorough comprehension and careful supervision by the physician who chooses to influence so important and complex a function as coagulation.

What is "effective" drug dose, or the "best" level at which prothrombic activity* should be kept for effective but safe therapy? There is at present no unequivocal answer to these questions. I do know, however, that when one-stage prothrombic activity is reduced below 10 per cent of normal, thrombin formation is markedly slowed and reduced. In my opinion, furthermore, a level of 5 to 10 per cent† of normal is reasonably safe, *if all other hemostatic functions are normal.* When the prothrombic activity drops below this value hemorrhage is likely to ensue.

Worthy of mention, in view of the widespread use of anticoagulants in myocardial infarction, are reports of fatal hemopericardium, which occurred in some cases in which pericarditis appeared as a prominent feature.[238] In the decision whether anticoagulants should be used, this and other complications must be weighed against the risks of thromboembolic disease.

As already stated, the dose of drug required to attain the desired prothrombin level depends on several variables, not the least being the weight of the patient. Another is drug absorption. One advance is the development of a water-soluble derivative‡ that can be given parenterally, thus obviating uncertain absorption in patients with vomiting or other disorders.[236,237] Another important advance is demonstration of the superiority of vitamin K_1 over the water-soluble preparations in rectifying drug-induced prothrombinopenia. The quickest way to correct the defect, however, is prompt transfusion with blood or plasma. Bank blood is just as effective as fresh material.

Heparin. Much of the newer knowledge regarding heparin has already been described. Particularly pertinent at this point is the immediacy of effect, its marked antithrombic and antithromboplastic activity, its disappearance and inactivation within a few hours and its immediate neutralization by protamine sulfate. Heparin acts in an entirely different manner from the coumarin drugs. Its effect is directly correlated with its concentration in the blood.[239] Moreover, when it is used in practice, its over-all interference with clotting is generally greater than that induced with prothrombinopenic agents: a clotting time of twenty to forty minutes obtained with heparin reflects the net effective elaboration, in that time, of much less than 1 unit of thrombin per cubic centimeter of blood.§ This is in sharp contrast to the usually normal clotting time (eight to fourteen minutes) of blood from subjects given Dicumarol, reflecting substantially more, and faster, thrombin formation. Experimental evidence suggests that heparin blocks induced intravascular clotting in dogs better than Dicumarol.[232] Whether heparin is more effective *clinically* has not yet been decided.

Although several materials have been synthesized that simulate the action of heparin (such as Paritol and dextran sulfate), none have yet proved safe for clinical use.

Certain practical points in the use of these anticoagulants deserve mention. The expense of repeated prothrombin determinations, essential when coumarin drugs are used, is about balanced by the high cost of heparin. When this anticoagulant is used determinations of the clotting time before each dose (every four to six hours) is not necessary — once daily should be adequate, but the tests should be done meticulously.[13] This is also true of obtaining the blood sample for prothrombin determination (when prothrombinopenic drugs are used). Poor technic can lead to wrong interpretations, with disastrous sequelae.

The following point deserves utmost emphasis: *anticoagulant therapy should not be used until the physician is sure that his patient has a normal hemostatic mechanism.* This need not entail extensive studies. A carefully taken history and carefully performed physical examination, observation of a blood film for platelets, determination of the bleeding time, plasma prothrombic activity and residual serum prothrombin (prothrombin consumption) and simple, informed inspection of the clot will in most cases disclose existing coagulation defects.¶

The procedure for intravenous administration of heparin‖ has recently been greatly simplified by use

*The term "prothrombic activity" refers to the over-all ability of the blood to form thrombin with thromboplastin. It reflects the level of prothrombin, serum prothrombin conversion accelerator, accelerator globulin and fibrinogen.[15] The first two are profoundly affected by the prothrombinopenic agents.

†This figure is based on certain methods for prothrombin determination.[13,15] Other "safe" levels described in the literature are based on other methods.

‡3-(phenyl-B-acetylethyl)-4-hydroxycoumarin (Coumadin) sodium (Warfarin Sodium), available from Endo Products, Incorporated, Richmond Hill, New York.

§Normal blood makes about 150 units of thrombin per cubic centimeter in forty minutes. Blood after administration of Dicumarol, containing 10 per cent prothrombin activity, makes about 10 units of thrombin in this time.

¶To explain why a clotting time is not included attention is again called to the fact that profound coagulation defects, concerned with disturbed thromboplastin elaboration, may hide behind a normal clotting time, as pointed out above in the discussion of clinical considerations of prothrombin conversion to thrombin. The prothrombin consumption test is far more valuable than the clotting time in disclosing them.

‖Other routes of heparin administration have been employed. Subcutaneous and intramuscular injections[240] are considered less effective, and the results irregular,[241] and they are frequently associated with local pain and hematomas.[241,242] Sublingual administration of heparin[243] appears to be ineffective.[244]

of a fine inlying plastic catheter, easily inserted into a superficial vein by an ordinary needle at the first venipuncture.[245] This has eliminated the discomfort of repeated venipunctures and has preserved accessible veins for later contingencies. Clearly, heparin is best suited for hospitalized patients.

In judging progress of the disease and deciding when anticoagulant therapy should be discontinued, one can be guided only by clinical criteria since there is no reliable test for thromboembolism. And these clinical criteria are not too reliable owing to the paucity of symptoms and signs. It is hoped that direct experimental study will help solve this problem. In the meantime, with each reappraisal of the question, the recommended therapeutic interval keeps rising; it is now held to be no less than two weeks, and preferably three. Also important to consider is the "rebound" phenomenon — that is, the development of abnormally high levels of certain clotting factors such as prothrombin, when anticoagulant therapy is terminated. This may contribute to a hypercoagulable state. Such observations speak for gradual reduction of therapy rather than sudden cessation.

Clot-dissolving agents — trypsin. Normal plasma contains a fibrinolytic mechanism presumably aimed at clot dissolution and recanalization of occluded vessels (Fig. 1), and it is well known that the proteolytic enzyme, trypsin, will lyse fibrin clots and destroy fibrinogen in vitro. The availability of highly purified material has led to renewed interest in its therapeutic use in thrombotic disease by intravenous administration, and beneficial results have been claimed.[246] This could not be confirmed, however, on experimentally induced intravascular clots.[247-250] In fact, infusions of trypsin actually induced extension of these clots[247,248] and caused profound disturbances varying from incoagulability to widespread intravascular thrombosis, depending on the amount of material administered and the velocity of its infusion.[249] Other serious abnormalities were observed.

Although the use of purified preparations of the naturally occurring fibrinolytic agents (plasminogen plasmin) warrants further exploration[251] the therapeutic approach with trypsin does not appear promising. Conceivably, it may even be harmful by inducing extension of a pre-existing venous thrombus and by causing its tail, growing centrally and floating freely in the venous blood, to break off, resulting in embolization. This complication has actually been observed during trypsin therapy.[251]

> The search for Truth is in one way hard and in another easy. For it is evident that no one can master it fully nor miss it wholely. But each adds to our knowledge of Nature, and from all the facts assembled there arises a certain grandeur . . . (Aristotle)

References

162. Landwehr, G., Lang, H., and Alexander, B. Congenital hypoprothrombinemia: case study with particular reference to role of nonprothrombin factors in conversion of prothrombin. *Am. J. Med.* **8**:255-259, 1950.
163. Biggs, R., and Douglas, A. S. Measurement of prothrombin in plasma: case of prothrombin deficiency. *J. Clin. Path.* **6**:15-22, 1953.
164. Jürgens, R. Wirkung von Vitamin K₁ auf die Dicumarol — Hypoprothrombinämie und die Acceleratorfaktoren am lebergeschädigten Kaninchen und nach Leberextirpation an der Katze. *Acta haemat.* **7**:143-156, 1952.
165. Alexander, B., and Goldstein, R. Coagulation defect in hepatic disorders: deficiency of prothrombin-conversion accessory substances. *J. Clin. Investigation* **29**:795, 1950.
166. Stefanini, M. Hemorrhagic diathesis of liver dysfunction and obstructive jaundice. In *Proceedings of the Third International Society of Hematology, Cambridge, England, 1950.* Edited by C. V. Moore. 593 pp. New York: Grune & Stratton, 1951.
167. Izarn, P., and Mathieu, M. L'hypoprothrombinémie des hépatiques: sa fréquence, ses causes, sa place dans la pathogénie des hémorragies. *Rév. internat. d' hépatol.* **2**:783-813, 1952.
168. Witte, S. P., and Dirnberger, P. Klinische Untersuchungen über die Gerinnungsfaktoren Prothrombin, Faktor V und Faktor VII bei Lebererkrankungen und ihre Beeinflussung durch Vitamin K₁ und Synka-Vit. *Klin. Wchnschr.* **31**:781-787, 1953.
169. Frank, E. D., Frank, H. A., and Fine, J. Traumatic shock. XVII. Plasma fibrinogen in hemorrhagic shock in dog. *Am. J. Physiol.* **162**:619-631, 1950.
170. *Idem.* Traumatic shock. XVIII. Plasma prothrombin activity in hemorrhagic shock in dog. *Am. J. Physiol.* **167**:499-507, 1951.
171. Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L. Occurrence of fibrinolysin in shock, with observations on prothrombin time and plasma fibrinogen during hemorrhagic shock. *Am. J. M. Sc.* **211**:88-96, 1946.
172. Larrieu, M. J., Soulier, J. P., and Minkowski, A. Le sang du cordon ombilical: étude complète de sa coagulabilité; comparaison avec le sang maternel. *Études néonatales* **1** (No. 1):39-60, 1952.
173. Loeliger, A., and Koller, F. Behavior of factor VII and prothrombin in late pregnancy and in newborn. *Acta haemat.* **7**: 157-161, 1952.
174. Van Creveld, S., et al. Proconvertin content in blood of newborn full-term and premature infants. *Études néonatales* **3** (No. 1):53-61, 1954.
175. Astrup, T., and Darling, S. Antithrombin and heparin. *Naturwissenschaften* **29**:300, 1941.
176. *Idem.* Measurement and properties of antithrombin. *Acta physiol. Scandinav.* **4**:293-308, 1942.
177. Seegers, W. H. Multiple protein interactions as exhibited by blood clotting mechanism. *J. Phys. & Colloid Chem.* **51**:198-206, 1947.
178. Quick, A. J., and Favre-Gilly, J. Fibrin, factor influencing consumption of prothrombin in coagulation. *Am. J. Physiol.* **158**: 387-395, 1949.
179. MacFarlane, J. C. W. Serum-antithrombin level in fibrocystic disease of pancreas. *Lancet* **2**:311-314, 1952.
180. Innerfield, I., Angrist, A., and Boyd, L. J. Plasma antithrombin titer in incipient and advanced liver failure. *Gastroenterology* **20**: 417-429, 1952.
181. Perlick, E. Zur klinischen Bedeutung des Plasmaantithrombins. *Arztl. Forsch.* **6**:49-51, 1952.
182. Innerfield, I., Angrist, A., and Benjamin, J. W. Antithrombin titer in acute pancreatitis. *Am. J. Med.* **12**:24-33, 1952.
183. Innerfield, I., and Angrist, A. Plasma antithrombin determination: new test for cancer of pancreas associated with jaundice. *Am. J. M. Sc.* **223**:422-428, 1952.
184. Morrison, P. R., Edsall, J. T., and Miller, S. G. Preparation and properties of serum and plasma proteins. XVIII. Separation of purified fibrinogen from fraction I of human plasma. *J. Am. Chem. Soc.* **70**:3103-3108, 1948.
185. Oncley, J. L., Scatchard, G., and Brown, A. Physical-chemical characteristics of certain of proteins of normal human plasma. *J. Phys. & Colloid Chem.* **51**:184-198, 1947.
186. Brand, E., and Edsall, J. T. Chemistry of proteins and amino acids. *Ann. Rev. Biochem.* **16**:223-272, 1947.
187. Ferry, J. D., and Morrison, P. R. Preparation and properties of serum and plasma proteins. VIII. Conversion of human fibrinogen to fibrin under various conditions. *J. Am. Chem. Soc.* **69**: 388-400, 1947.
188. Edsall, J. T., and Lever, W. F. Effect of ions and neutral molecules on fibrin clotting. *J. Biol. Chem.* **191**:735-756, 1951.
189. Waugh, D. F., and Livingstone, B. J. Clotting time and reaction velocity in interaction of bovine fibrinogen and thrombin. *Science* **113**:121-124, 1951.
190. Waugh, D. F., and Livingstone, B. J. Kinetics of interaction of bovine fibrinogen with thrombin. *J. Phys. & Colloid Chem.* **55**: 1206-1218, 1951.
191. Bailey, K., Bettelheim, F. R., Lorand, L., and Middlebrook, W. R. Action of thrombin in clotting of fibrinogen. *Nature* (London) **167**:233, 1951.
192. Lorand, L. Fibrino-peptide: new aspects of fibrinogen-fibrin transformation. *Nature* (London) **167**:992, 1951.
193. Laki, K. Clotting of fibrinogen. *Blood* **8**:845, 1953.
194. Lorand, L. Interaction of thrombin and fibrinogen. *Physiol. Rev.* **34**:742-752, 1954.
195. Sherry, S., Troll, W., and Glueck, H. Thrombin as proteolytic enzyme. *Physiol. Rev.* **34**:736-741, 1954.
196. Lawson, H. A. Congenital afibrinogenemia. *New Eng. J. Med.* **248**:552-554, 1953.
197. Seegers, W. H., and Schneider, C. L. Nature of blood coagulation mechanism and its relationship to some unsolved problems in obstetrics and gynecology. *Am. J. Obst. & Gynec.* Supp. **61A**: 469-482, 1951.
198. Reid, D. E., Weiner, A. E., and Roby, C. C. I. Intravascular clotting and afibrinogenemia, presumptive lethal factors in syndrome of amniotic fluid embolism. II. Incoagulable blood in severe premature separation of placenta: method of management. III. Maternal afibrinogenemia associated with long-standing intrauterine fetal death. *Am. J. Obst. & Gynec.* **66**:465-506, 1953.
199. Ratnoff, O. D., and Vosburgh, G. J. Observations on clotting defect in amniotic-fluid embolism. *New Eng. J. Med.* **247**:970-973, 1952.

200. Mathey, J., Daumet, P., Soulier, J. P., Le Bolloc'h, A. G., and Fayet, H. Hémorragies graves au cours d'interventions thoraciques par incoagulabilité sanguine dûe à la fibrinolyse. *Mém. Acad. de chir.* **76**:977-986, 1950.
201. Conference on fibrinolysis. *Nat. Research Council Bull.* (Nov. 18), 1952. Pp. 111-187.
202. Penn, S. R., and Walker, J. H. Defective blood coagulation following pulmonary surgery. *New Eng. J. Med.* **250**:764, 1954.
203. Coon, W. W., and Hodgson, P. E. Fibrinolysis in surgery patients. I. Possible relationship to hemorrhagic diathesis. *Surg., Gynec. & Obst.* **95**:717-724, 1952.
204. Christensen, L. R., and MacLeod, C. M. Proteolytic enzyme of serum: characterization, activation, and reaction with inhibitors. *J. Gen. Physiol.* **28**:559-583, 1945.
205. Astrup, T. Fibrinolytic enzymes. In *Blood Clotting and Allied Problems: Transactions of the first conference.* Edited by J. E. Flynn. 179 pp. New York: Josiah Macy, Jr. Foundation, 1948. Pp. 28-37.
206. Macfarlane, R. G., and Biggs, R. Fibrinolysis: its mechanism and significance. *Blood* **3**:1167-1187, 1948.
207. Loomis, E. Fibrinolysin and antifibrinolysin: proteolytic enzyme system in blood. In *Blood Clotting and Allied Problems: Transactions of the fifth conference.* Edited by J. E. Flynn. 368 pp. New York: Josiah Macy, Jr. Foundation, 1952. Pp. 280-328.
208. Virchow, R. Cited by Eberth, J. C., and Schimmelbusch, C. Experimentelle Untersuchungen über Thrombose. *Virchows Arch. f. Path. Anat.* **103**:39-87, 1886.
209. Barondess, J. A. Thrombotic thrombocytopenic purpura: review of literature and report of three cases. *Am. J. Med.* **13**:294-310, 1952.
210. Ingram, G. I. C., Biggs, R., and Armitage, P. Laboratory tests for incipient thrombosis. *J. Clin. Path.* **6**:46-51, 1953.
211. Zucker, M. B. Platelet agglutination and vasoconstriction as factors in spontaneous hemostasis in normal, thrombocytopenic, heparinized and hypoprothrombinemic rats. *Am. J. Physiol.* **148**:275-288, 1947.
212. Fulton, G. P., and Akers, R. P. Blood flow in transillumined membranes after stasis and under pathological and traumatic conditions. *Federation Proc.* **9**:46, 1950.
213. Lutz, B. R., Fulton, G. P., and Akers, R. P. White thromboembolism in hamster cheek pouch after trauma, infection and neoplasia. *Circulation* **3**:339-351, 1951.
214. Warren, K. Postoperative thrombophilia. *New Eng. J. Med.* **249**: 99-106, 1953.
215. Paterson, J. C., and McLachlin, J. Precipitating factors in venous thrombosis. *Surg., Gynec. & Obst.* **98**:96-102, 1954.
216. Wright, H. P., Osborn, S. B., and Edmonds, D. G. Effects of postoperative bed rest and early ambulation on rate of venous blood flow. *Lancet* **1**:22-25, 1951.
217. Jones, W. T. On state of blood and blood-vessels in inflammation. *Guys Hosp. Rep.* (Second Series) **7**:1-100, 1850.
218. Bizzozero, J. Über einen neuen Formbestandtheil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung. *Virchows Arch. f. Path. Anat.* **90**:261-332, 1882.
219. O'Neill, J. F. Effects on venous endothelium of alterations in blood flow through vessels in vein walls, and possible relation to thrombosis. *Ann. Surg.* **126**:270-288, 1947.
220. Samuels, P. B. Relation of venous endothelium to thrombosis. *Proc. Roy. Coll. Physicians & Surgeons, Canada,* October, 1953. Pp. 75-98.
221. Wright, H. P. Changes in adhesiveness of blood platelets following parturition and surgical operations. *J. Path. & Bact.* **54**: 461-468, 1942.
222. Wright, H. P. Characteristics of blood platelets: their significance in thrombus formation. In *Blood Clotting and Allied Problems: Transactions of the fourth conference.* Edited by J. E. Flynn. 272 pp. New York: Josiah Macy, Jr. Foundation, 1951. Pp. 119-142.
223. Owren, P. Prothrombin and accessory factors: clinical significance. *Am. J. Med.* **14**:201-216, 1953.
224. Wessler, S. Experimental intravascular thrombosis induced by serum fractions containing serum prothrombin conversion accelerator (SPCA). *Federation Proc.* **12**:152, 1953.
225. Wright, I. S., Marple, C. D., and Beck, D. F. Report of Committee for Evaluation of Anticoagulants in Treatment of Coronary Thrombosis with Myocardial Infarction: progress report on statistical analysis of first 800 cases studied by this committee. *Am. Heart J.* **36**:801-815, 1948.
226. *Idem. Myocardial Infarction: Its clinical manifestations and treatment with anticoagulants: a study of 1031 cases.* 656 pp. New York: Grune & Stratton, 1954.
227. Anderson, G. M., and Hull, E. Effect of dicumarol upon mortality and incidence of thromboembolic complications in congestive heart failure. *Am. Heart J.* **39**:697-720, 1950.
228. Levinson, D. C., and Griffith, G. C. Evaluation of anticoagulant therapy in congestive heart failure. *Circulation* **4**:416-419, 1951.
229. Russek, H. I., and Zohman, B. L. "Selective" vs. "routine" use of anticoagulants in acute myocardial infarction. *J.A.M.A.* **158**: 1130-1132, 1954.
230. Schnur, S. Current dispute concerning anticoagulants in acute myocardial infarction. *J.A.M.A.* **156**:1127-1130, 1954.
231. DeBakey, M. E. Critical evaluation of problem of thromboembolism. *Internat. Abstr. Surg.* **98**:1-27, 1954.
232. Wessler, S. Studies in intravascular coagulation. II. Comparison of effect of dicumarol and heparin on clot formation in isolated venous segments. *J. Clin. Investigation* **32**:650-654, 1953.
233. Douglas, A. S. Coagulation defect in tromexan therapy. *Lancet* **2**:761, 1952.
234. Hunter, R. B., and Walker, W. Control of anticoagulant therapy in myocardial infarction. *Brit. M. J.* **2**:197-199, 1954.
235. Walker, W., and Hunter, R. B. Action of coumarin anticoagulants on possible new serum clotting factor. *Nature* (London) **173**:1192, 1954.
236. Shapiro, S. Warfarin sodium derivative (Coumadin sodium): intravenous hypoprothrombinemia-inducing agent. *Angiology* **4**:380-390, 1953.
237. Clatanoff, D. V., Triggs, P. O., and Meyer, O. O. Clinical experience with coumarin anticoagulants warfarin and warfarin sodium. *Arch. Int. Med.* **94**:213-220, 1954.
238. Goldstein, R., and Wolff, L. Hemorrhagic pericarditis in acute myocardial infarction treated with bishydroxycoumarin. *J.A.M.A.* **146**:616-621, 1951.
239. Monkhouse, F. C., MacMillan, R. L., and Brown, K. W. G. Relation between heparin blood level and blood coagulation times. *J. Lab. & Clin. Med.* **42**:92-97, 1953.
240. Loewe, L., Rosenblatt, P., and Hirsch, E. Venous thromboembolic disease. *J.A.M.A.* **130**:386-393, 1946.
241. Jorpes, E. Recent trends in anticoagulant therapy of thrombosis. *Acta haemat.* **7**:257-271, 1952.
242. Fantl, P., and Ebbels, L. Experience with intramuscular administration of heparin preparations: comparison between aqueous and retard heparin. *Australian Ann. Med.* **1**:135-139, 1952.
243. Litwins, J., Vorzimer, J. J., Sussman, L. N., Applezweig, N., and Etess, A. D. Sublingual administration of heparin. *Proc. Soc. Exper. Biol. & Med.* **77**:325, 1951.
244. McDevitt, E., Huebna, R. D., and Wright, I. S. Ineffectiveness of heparin by sublingual administration. *J.A.M.A.* **148**:1123, 1952.
245. Wessler, S., and Fischbein, J. W. Improved method for intravenous administration of heparin: its clinical application. *New Eng. J. Med.* **250**:860-863, 1954.
246. Innerfield, I., Angrist, A., and Schwarz, A. Parenteral administration of trypsin: clinical effect in 538 patients. *J.A.M.A.* **152**: 597-605, 1953.
247. Wessler, S. Experimentally produced phlebothrombosis in study of thromboembolism. *J. Clin. Investigation* **32**:610, 1953.
248. *Idem.* Studies in intravascular coagulation. III. Pathogenesis of serum-induced venous thrombosis. *J. Clin. Investigation* (in press).
249. Taylor, A., Overman, R. S., and Wright, I. S. Studies with crystalline trypsin: results and hazards of intravenous administration and its postulated role in blood coagulation. *J.A.M.A.* **155**: 347-351, 1954.
250. Sherry, S., Titchener, L. G., Wasserman, P., and Troll, W. Enzymatic dissolution of experimental arterial thrombi in dog by trypsin, chymotrypsin and plasminogen activators. *J. Clin. Investigation* **33**:1303-1313, 1954.
251. Seligman, B. Pulmonary embolism complicating trypsin therapy. *New Eng. J. Med.* **250**:23, 1954.

MEDICAL INTELLIGENCE

DIGITALIS IN ACUTE MYOCARDIAL INFARCTION

NORMAN H. BOYER, M.D.*

BOSTON

A DECADE ago the general subject of cardiogenic shock was reviewed in this journal.† The principal interest in that effort centered around "shock" in myocardial infarction. The evidence available was interpreted as indicating that this shocklike state was mainly, if not wholly, due to failure of the left ventricle and that its presence or absence depended on the quantity and quality of uninfarcted myocardium. Whatever has transpired since that time, both from personal experience and from medical reports, has served to strengthen, rather than to alter, this view.

Obviously, the quantity of remaining muscle is largely beyond medical control, although therapeutic efforts might salvage a rim of muscle around the periphery of the infarct. On the other hand, it was suggested that the quality of uninfarcted portions of the heart might be improved. Two controversial points were discussed, one being the use of pressor drugs and the other the possible value of digitalis.

It was pointed out in the earlier paper that much of the fear of using digitalis in the presence of fresh myocardial infarction rested on insecure ground, being the result of animal experimentation concerned with *toxic* or *lethal* amounts of the drug, combined with liberal amounts of sometimes fallacious speculation. For several years before the publication of the review article and on the basis of a conviction that patients' lives were being lost because digitalis was withheld until a stage had been reached where no one could quarrel with its use, I had begun a cautious clinical appraisal. Some years later fate delivered an interesting, if not crucial, experiment: a forty-five-year-old man was admitted to the hospital with a large anterior-wall infarction. By the day after admission the temperature had risen to 103°F., and the white-cell count to over 35,000. Electrocardiograms supported these other evidences of a large infarct. By afternoon of the second day the pulse had risen to 140 (sinus rhythm), and the blood pressure had fallen progressively, along with the development of pallor, sweating and basal rales. He was given 1.2 mg. of lanatoside C intravenously, and orders were left that an additional 0.4 mg. was to be given intramuscularly in four hours. By mistake he was given 0.4 mg. every four hours until the error was discovered on the following day. At that time he had received a total of 3.6 mg. of glycoside. Here, then, was a man seriously ill with a large myocardial infarct who had received a good deal more digitalis than would customarily be given. The fact that the patient recovered and is well eight years later is not the main point of the story, nor is it meant to convince the skeptical. But, for me, fear of digitalis under these circumstances declined to the vanishing point. I have since used it freely and have yet to encounter any ill effects directly attributable to the drug.

In a series of 50 consecutive patients with proved fresh myocardial infarction who received digitalis the mortality was 16 per cent. This was a heterogeneous group and included patients with "shock," congestive heart failure and atrial fibrillation, as well as some with lesser evidence of weakness of the left ventricle. These patients showed sinus tachycardia, or a rising heart rate, either alone or in combination with pulsus alternans, a loud gallop or accentuation of the pulmonic second sound.

This mortality is not cited as proof that digitalis therapy favorably influenced the course of the disease, although the impression that it did is strong indeed, since none of these cases could be called "favorable." However, the prognosis of myocardial infarction is determined by so many variables that a large series of patients with carefully matched controls would be needed to settle this point. It seems to be morally indefensible to withhold digitalis, when indicated, for the sake of obtaining such controls.

What, seemingly, can be deduced is that digitalis, carefully used, is rarely, if ever, accompanied by the dire consequences freely predicted in medical writings. Toxicity should, of course, be avoided, and a rapidly dissipated preparation should be employed, at least initially. In this connection it should be emphasized that longer-acting preparations cannot be used to maintain the action of a rapidly dissipated one — a very common error — since the effect of the priming dose of, for example, lanatoside C, will have disappeared within forty-eight to seventy-two hours. A satisfactory method of maintaining digitalis action for a few days is the intramuscular injection of, on the average, 0.4 mg. of lanatoside C daily. If more prolonged administration seems necessary the patient may be started on a program of slow digitalization by mouth beginning twenty-four hours after the last parenteral dose of glycoside. Digitalis leaf, 0.1 gm. three times a day for four or five days, or gitalin, 0.5 mg. on the same schedule, has been used. During this redigitalization, signs of overdosage in the beginning or of underdosage in the middle or near the end of the period must be carefully evaluated.

*Assistant professor of medicine, Boston University School of Medicine; physician-in-charge, Cardiac Clinic and Electrocardiographic Laboratory, Massachusetts Memorial Hospitals.

†Boyer, N. H. Cardiogenic shock. *New Eng. J. Med.* **230**:226-229 and 256-260, 1944.

Contrary to the opinion sometimes expressed, it has not been necessary to use quinidine or Pronestyl along with digitalis. If cardiac irritability is already present one or the other is indicated in any case.

No doubt this report will seem superfluous to some readers, but there is still great reluctance to use digitalis in the presence of fresh myocardical infarction. It seems timely for someone to report the use of digitalis freely under these circumstances. I believe that it is frequently indicated in myocardial infarction and may, indeed, be life saving. Certainly, it has not proved to be as lethal as some seem to believe.

29 Bay State Road

BY THE LONDON POST

From the Editorial Chair

JOHN LISTER, M.D.

LONDON, ENGLAND

IT was a unique occasion when four leading medical editors recently addressed the Royal Society of Medicine. They had been persuaded to leave the security of their editorial offices and brave the dangers of the speaker's rostrum to present to the Section of Medicine a symposium on the problems that face a medical editor.

The subject was opened by Dr. T. F. Fox, of the *Lancet,* who spoke with what Sir Henry Cohen described as characteristic lupine wit. He recalled that the *Lancet* was founded in 1823 by Thomas Wakley, who hoped that it would promote reform and disseminate knowledge. Indeed, he went further and wished the *Lancet* to publish a correct description of all important cases that might occur whether in England or in the "civilized continent." The task soon became too great for the *Lancet.* More and more journal space became necessary, and the functions of journals changed. The main function of a journal is now to record rather than to inform, and the tendency is for the journal to serve the producer rather than the consumer of the subject matter.

Publishers have not been slow to respond to the need for journals. There were 5000 within the first thirty years of medical journalism, and today the proliferation of medical journals has almost become a malignant process, which has been described by the term "journalistic blastoma." For the seeker after knowledge the cumulative quarterly index has become as important as the telephone directory, and even with its help there is still a great danger that medical pearls of great price are being cast before regular subscribers but remain hidden from those requiring them to complete their necklaces of knowledge.

Dr. Fox wondered whether there might not be a better way of facilitating the extension of knowledge than by allowing the malignant proliferation of journals to continue. He thought that perhaps an editorial board might be set up for each specialty. Authors could then submit their work to the board, which would arrange to circulate abstracts of all worthy material and compile a microfilm library of the original articles. On further reflection, however, he thought that reading a journal by the fire would be a more pleasant way of spending an evening than digesting desiccated knowledge on cards or projecting microfilm on the wall. He thought that the great value of a journal was that it encouraged casual reading, whose purpose was to be able to skip. Traveling in a train anonymously, he had recently seen a skilled reader run through the *Lancet* in as little as seventy seconds. Of course, this was not surprising because he agreed that nine tenths of the published material in the *Lancet* is of no value to the average subscriber. For this he did not apologize because even a glance at the titles of the articles would give the reader an idea of what is going on. He regarded the *Lancet* as a general medical newspaper aiming at integrating a profession that is in danger of falling apart. The profession being composed of a body of doctors with basically common interests, each should be aware of what others are doing. Hence, in a general medical newspaper, there is a place not only for reports of cases and original work whether from home or abroad, but also for discussion of such problems as the organization of the profession and its relation to kindred professions. In this way the reader may receive a weekly dose of a general medical mixture, and medicine may become integrated and the physician may learn to guard his patients against disease and against the specialist.

Dr. A. M. Cooke, a member of the editorial board of the *Quarterly Journal of Medicine,* assured his audience that the medical editor was really the friend rather than the enemy of contributors. He had a duty to be the guardian of the standards of his journal and to be a guardian of posterity, but he also had a duty to help his authors to present and publish their material. In the early days of the *Quarterly Journal of Medicine* an author either had his article accepted in a curtly worded note or rejected in a charming letter from Osler that made him feel far better than if it had been accepted. Dr. Cooke urged authors never to write unless they had something worth saying, always to be brief and clear and above all to avoid slang and absurdities. As an extreme example of an absurdity he pointed out that the likening of an organ to the size of a Kansas sales-tax ticket could well be meaningless to readers living outside Kansas.

Dr. Thomson, of the *Practitioner,* spoke of the problem of selecting material for publication. To select wisely the editor must know what his readers want. In this connection he made a plea for the unorthodox view. Medicine is a living art and a living

science, and orthodoxy may not always be the best medium in which to fan the flame of progress. An open mind is required, and unorthodox views must be given a hearing — indeed, their expression may sometimes stimulate new thoughts on an old problem.

Dr. Thomson thought that editorial comment must at times be provocative and at times in the nature of a judicial summing up. When professional privileges are abused or professional freedom compromised there must be condemnation, for the medical editor can do much to maintain the ethical code. He must always be careful to do nothing that might resist progress.

The last speaker of the team was Dr. Hugh Clegg, the editor of the *British Medical Journal,* who remarked that the functions and standards of journals had both been discussed and the function of an editor outlined. He had been asked to comment on some of the current problems of the day. One of these was the volume of original articles offered for publication. Many were so bad that he often thought it would be fun to publish a journal for bad articles. In any case he thought that, in spite of the malignant nature of journalistic proliferation, it was preferable to start a journal in a subject than to establish a professorship. After all, if a journal is no good it will soon die, but if a professor is bad . . . He agreed that the articles in the *British Medical Journal* were often too learned for the middle-aged practitioner, but in the *Lancet* they were always so. Concerning the old controversy over whether book reviews should be signed or unsigned, he reminded the meeting that Dickens referred to anonymous reviewers as the "lice of literature" and agreed that any author whose book was unfavorably reviewed should have the satisfaction of knowing the reviewer's name — always on the assumption that he was not one of those difficult folk who never read books before reviewing them because it "biases one so."

There is no doubt that the evening was a great success. In the first place it was highly entertaining, but, more important, it emphasized the service that is being rendered by those back-room boys of the profession — the medical editors. Asked where they came from, Dr. Fox answered that he often wondered where they went to, but as far as his colleagues in the *Lancet* office were concerned, he thought they were sent from heaven. In this mood the meeting adjourned, the editors back to their offices and the clinicians and investigators back to their desks to write more and (the editors hope) better scientific papers.

MASSACHUSETTS PHYSICIANS ART SOCIETY

36. *"Edipus Complex"*

Published in *Parergon,* Volume 2, 1947. Reprinted by courtesy of Mead Johnson & Company.

Oil Painting by
NORMAN LENSON, M.D.
Brookline, Massachusetts

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41131

PRESENTATION OF CASE

First Admission. A sixty-two-year-old unemployed millworker entered the hospital because of abdominal pain and swelling.

About three weeks previously he first became aware of abdominal swelling and generalized abdominal pain, which occurred two or three times a day, began in the lower abdomen and radiated upward, and was partially relieved by defecation and urination. During this period he also experienced anorexia, eructations, weakness and fatigability, and noted "whisky-colored" urine. He had some shortness of breath after the abdominal swelling appeared. He noted no change in the color of the skin or stools. His diet had been "fair" although after he lost his job a year before admission his meals consisted largely of fruit and vegetables, being deficient in protein and calories. He denied any but slight social wine drinking.

He had been born in Sicily and had come to the United States thirty-three years before admission. He had had varicose veins and chronic ankle swelling for six years before admission.

Physical examination revealed a well nourished man in no distress. Several spider-like hemangiomas were present over the shoulders and back. The scleras were questionably icteric. The neck veins were minimally distended when he was sitting upright. Pulmonary findings were consistent with emphysema. The heart was not enlarged. The aortic second sound was greater than the pulmonic, and there were soft apical and aortic systolic murmurs. The abdomen was markedly protuberant, with a fluid wave and shifting dullness. The liver was not palpable, but several observers thought it was enlarged to percussion. The spleen was not palpable. No collateral venous pattern was seen. Bowel sounds were normal. Rectal examination revealed a slightly enlarged, smooth prostate. Both lower extremities demonstrated ++ to +++ pitting pretibial edema, with stasis dermatitis and a healed ulcer on the left. Neurologic examination was negative.

The temperature was 99.4°F., the pulse 110, and the respirations 24. The blood pressure was 135 systolic, 100 diastolic.

Urinalysis showed a specific gravity of 1.027, a + reaction for bile and 1 to 3 white cells per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 13.0 gm. per 100 cc. and a white-cell count of 3450, with 71 per cent neutrophils. The erythrocytes were slightly hypochromic. The bilirubin was 2.0 mg., the total protein 6.8 gm., with an albumin-globulin ratio of 4.6:2.2, the alkaline phosphatase 5.2 units, the cholesterol 133 mg. and the cholesterol esters 75 mg. per 100 cc.; the cholinesterase was 0.23 delta pH units per hour. Cephalin flocculation was +++ in twenty-four and forty-eight hours. The thymol turbidity was 3.5 units, and the prothrombin time 45 per cent of normal. Bromsulfalein retention was 31 per cent. The iron-binding capacity was 250 microgm. per 100 cc., with 40 per cent saturation. A stool guaiac test was negative. An electrocardiogram was within normal limits. X-ray films of the abdomen revealed a generalized haziness, which was probably due to fluid, an area of calcified lymph nodes on the right, and high leaves of the diaphragm; the spleen was thought to be enlarged, but no statement about the size of the liver was made. An x-ray film of the chest suggested slight cardiac enlargement. A gastrointestinal series demonstrated no definite varices and was otherwise negative. The venous pressure in the right arm was equivalent to 108 to 120 mm. of water, and the arm-to-tongue circulation time with sodium dehydrocholate was 14 seconds. The gall bladder was not visualized even with a double dose of Telepaque.

Shortly after admission a paracentesis yielded 3000 cc. of yellow fluid, having a specific gravity of 1.012 and containing 750 white cells per cubic millimeter and an equal number of red cells and with a total protein of 1.5 gm. per 100 cc. Cytologic studies and a cell block were negative for malignant cells. A culture was negative. Immediately after the paracentesis it still was not possible to palpate the liver or spleen. An aspiration liver biopsy was inadequate for diagnosis. Two white-cell counts on the peripheral blood were 4600 and 5400. On a high-vitamin, high-calorie, high-protein diet and ammonium chloride the patient improved, and he was discharged three weeks after admission.

Final admission (about three months later). A month after discharge when he was seen in the clinic his general course was thought satisfactory. The alkaline phosphatase had risen to 14.7 units per 100 cc., but the bilirubin and total protein were unchanged. However, when seen again a month later, he had gained 18 pounds since discharge, had reaccumulated

abdominal fluid despite adherence to the prescribed diet and was becoming increasingly anorectic. The alkaline phosphatase was 10.0 units per 100 cc., and the cholinesterase 0.17 delta pH units per hour. He reported to the clinic three weeks later because of extreme weakness. He had eaten well, adhering to the prescribed diet, until about two weeks previously. At that time, however, the abdominal pain returned, and because it was aggravated by eating he cut down markedly on the food intake. He was re-admitted to the hospital.

Physical examination was unchanged from the previous admission.

The temperature was 100°F., the pulse 100, and the respirations 24. The blood pressure was 140 systolic, 90 diastolic.

Urinalysis revealed a specific gravity of 1.024, a green test for sugar and an occasional red cell and white cell in the sediment; no bile was found. The hemoglobin was 14.6 gm. per 100 cc., and the white-cell count 7200, with 79 per cent neutrophils. The bilirubin was 2.7 mg., the total protein 6.4 gm., with an albumin-globulin ratio of 4.4:2.0, the nonprotein nitrogen 30 mg., the cholesterol 198 mg., the cholesterol esters 118 mg., the serum calcium 8.8 mg., the phosphorus 3.5 mg., and the alkaline phosphatase 8.5 units per 100 cc., and the sodium was 130 milliequiv., the potassium 5.0 milliequiv., the chloride 94 milliequiv., and the carbon dioxide 23 milliequiv. per liter; the cholinesterase was 0.11 delta pH units per hour. The fasting blood sugar was 129 mg.; a glucose tolerance test revealed a half-hour rise to 239 mg., with a gradual fall to 135 mg. per 100 cc. in three hours. Cephalin flocculation was ++ in twenty-four and forty-eight hours, and the prothrombin time 60 per cent of normal. A bromsulfalein test showed 15 per cent retention. Stool guaiac tests were repeatedly negative, as was a barium-enema examination. A gastrointestinal series revealed varices in the distal esophagus.

During paracentesis, done shortly after admission, 9 liters of fluid was removed. Afterward, an examiner felt a firm, smooth liver edge in the right epigastrium; the spleen was felt 2 fingerbreadths below the left costal margin, and the veins over the costal margins were described as "prominent." The total protein content of the ascitic fluid was 0.750 gm. per 100 cc. A cell block of the fluid once again revealed no malignant cells. The patient was again treated with a high-protein, high-calorie, high-vitamin, low-salt (500 mg.) diet and improved somewhat. He felt better after the second paracentesis on the third hospital day, at which time 3 liters of fluid was removed. Insulin (10 units daily) was started on the sixth hospital day. Ascitic fluid continued to accumulate rapidly, and on the tenth hospital day, during the third paracentesis, 2850 cc. of fluid was removed. The fluid had a specific gravity of 1.010 and contained 1840 cells per cubic millimeter, of which 140 were white cells, and a total protein of 1.0 gm. per 100 cc. A culture was negative. Peritoneoscopy the next day showed a "very hobnailed liver," but the biopsy specimen revealed no diagnostic abnormality, although it was stated that the biopsy was inadequate to rule out cirrhosis. Later that day a "flap" characteristic of liver disease developed, and he felt very weak and tired. It was believed that he was approaching liver coma, and ammonium chloride was stopped and the protein intake decreased from 90 to 50 gm. daily. A blood ammonia determination was 207 microgm. per 100 cc. (normal, 40 to 80 microgm.). Glutamic acid was started but without producing any change in the clinical picture. On the seventeenth hospital day the serum sodium determination was 108 milliequiv., the potassium 6.6 milliequiv., and the chloride 86 milliequiv. per liter, and the nonprotein nitrogen was 40 mg. per 100 cc. On the next day he ate a full breakfast but that afternoon was noted to have cool, clammy extremities, and the neck veins were distended to the angle of the jaw when he sat upright; bilateral basal wet rales were heard to the angles of the scapulas, with subcutaneous emphysema over the chest and abdomen. Despite rigorous measures he progressively deteriorated over the next few days, once again approaching coma, and died on the twenty-third hospital day.

Differential Diagnosis

Dr. Earle M. Chapman*: " . . . after he lost his job a year before admission his meals consisted largely of fruit and vegetables, being deficient in protein and calories." I might comment on the wisdom of the body. It should be noticed that he selected a diet deficient in protein and that, as circumstances developed, this diet was probably right for him.

May I see the x-ray films?

Dr. C. C. Wang: The chest films on admission show nothing remarkable in either lung field; the heart is somewhat enlarged in the region of the left ventricle, and the aorta is quite tortuous. Both leaves of the diaphragm are higher than normal, and in the lateral projection one can see lobulations in the mid-portion of the diaphragm. The significance of that I do not know. A gastrointestinal series demonstrates nothing unusual in the stomach and duodenum.

Dr. Chapman: Is there any lesion in the second portion of the duodenum particularly?

Dr. Wang: No; there is nothing unusual — no widening of the loop of the duodenum and no extrinsic or intrinsic defect. The esophagus shows tortuous, widened folds.

Dr. Chapman: Do you interpret those as varices?

Dr. Wang: They are certainly suggestive of varices.

Dr. Chapman: Is that a later film? Later, varices were said to be seen, but at first they were not noted.

Dr. Wang: The varices were present on the first examination. The spleen is markedly enlarged, and

*Physician, Massachusetts General Hospital.

the liver is not. A barium-enema examination is negative.

DR. CHAPMAN: It is interesting that, after paracentesis, a spleen that large was not felt.

It has taken me almost twenty minutes to read the imposing array of laboratory evidence. Yet with all that evidence, I can do no better than the old fashioned country physician, who would undoubtedly have said, "The patient has a very sick liver, he is not going to live long; do not feed him too much meat, for it is not good for him." With all this evidence what diagnosis can I make that would be better than the country physician's? I can speculate about it. I regret that the two schools of diagnostic proof — the needle biopsy and the peritoneoscopy — that are represented here by Dr. Point and Dr. Benedict failed to make a diagnosis. I have often heard Dr. Benedict say that one should not stab around in the dark with a needle, but should let him go in with the peritoneoscope and he would find out what was wrong with the patient.

DR. EDWARD B. BENEDICT: I did find out exactly: there was a hobnail liver.

DR. CHAPMAN: The next question, then, is what hobnailed the liver. Dr. Benedict did not tell us that on the biopsy.

DR. BENEDICT: You mean Dr. Castleman did not tell us.

DR. CHAPMAN: I might speculate about the cause of the hobnail liver. Laboratory investigations have always been aimed at bringing out patterns of liver function that would help us to distinguish the types of liver disease. Here, most of the laboratory evidence is conflicting, and one cannot tell what type of liver disease was present. A clinician, on the basis of the history and findings, could do as well in distinguishing the type of disease present. The patient had had varicose veins and chronic ankle swelling for six years; he was an Italian, and he admitted some wine drinking — probably he had some portal cirrhosis. Yet something acute happened about four months before admission and was associated with a large spleen and a hobnail type of liver. The Service apparently was searching for carcinoma, possibly in the digestive tract, but no such lesion was found. There apparently was no obstructing lesion in the head of the pancreas with metastases to the liver.

The patient could have had malignant lymphoma. The nodules that were seen could have been lymphomatous nodules. Indeed, the size of the spleen would fit with that. This new test, the serum cholinesterase, has been done only recently in this hospital, and it may be a valuable test although there has been some skepticism about it. The one consistent change in the welter of laboratory tests was that the serum cholinesterase fell at each observation. Molander, Freedman and LaDue[1] reported that these low values were seen particularly in metastatic carcinoma or lymphoma complicated by a spread of the disease to the liver. I think a malignant lesion was present in this patient. Whether it was carcinoma or lymphoma is only clinical conjecture because there was no positive evidence for either. The diagnosis of lymphoma is the more attractive one, and I suspect that he probably had some underlying portal cirrhosis and a great deal of lymphatic spread of the lymphoma through the liver.

I might comment on the high-protein diet, which, as I indicated before, I think was an unwise choice and perhaps led to the cholemia or hastened its appearance. The ammonium and the high protein perhaps combined to produce the syndrome that McDermott and Adams[2] have clarified as the cholemic picture, which probably is caused by failure of the liver to deaminize the protein in the body. When the physicians attempted to treat the cholemia it was at an irreversible stage; all the indexes of electrolyte contents and liver function were those of a terminal stage. The patient died in circulatory collapse and cholemia. I am puzzled about the source of the subcutaneous emphysema — unless it came from the instrumentation procedures.

DR. BENJAMIN CASTLEMAN: Dr. Chapman, will you amplify the reasons why the physicians who reported about the cholinesterase determination found these changes in neoplastic disease. Did they have controls with cirrhotic livers? What was the basis of the changes?

DR. CHAPMAN: It was an empirical observation. They admitted that they also had variable results. The fall in the cholinesterase was observed in acute parenchymatous liver disease, but variable values were also noted in chronic cirrhosis. I do not think they gave any clear reasons for their results. This is a relatively new test, — it was only introduced by Michel in 1949, — and it has not yet received wide clinical application.

DR. REED HARWOOD: Did you consider hepatoma?

DR. CHAPMAN: If the patient had had a hepatoma he would have had a single large expanding lesion and would not have had the hobnailings that Dr. Benedict observed. I think such a lesion in the liver would have been palpable; the liver had not been palpable and never reached any great size. The spleen was much larger than it usually is with cirrhosis.

DR. CASTLEMAN: Most hepatomas occur in patients with pre-existing cirrhosis so that the hobnailing that Dr. Benedict saw could have been a portal cirrhosis underlying a hepatoma.

DR. HELEN S. PITTMAN: Dr. Tracy B. Mallory always talked about white-cell counts in the differential diagnosis in cirrhosis. This man had a low white-cell count of 3500 on the first admission and 7200 on the second; both times there were more than 70 per cent neutrophils. Does that argue in any way against cirrhosis?

DR. CASTLEMAN: Many patients with cirrhosis have low white-cell counts.

DR. ROY VAGELOS: I saw this patient on the ward. The subcutaneous emphysema followed the peritoneoscopy and apparently was caused by air blown in under the skin. The high-protein diet was instituted because on admission the patient had primarily a large amount of ascites and the chemical determinations did not indicate that he had severe active parenchymal disease — the albumin was high, the globulin was low, and the bromsulfalein retention was not particularly abnormal. It was believed that, besides the portal cirrhosis, he had a secondary portal-vein thrombosis, since the portal hypertension was far out of proportion to the amount of apparent liver disease. We believed he might do very well with a shunt procedure in that case. Ascites was the primary complaint and was what brought him into the hospital.

DR. CASTLEMAN: Do you mean a portacaval shunt?

DR. VAGELOS: Yes; we thought that if we could improve the condition of the liver and could prove the presence of portal-vein thrombosis, a shunt would be indicated.

DR. CHAPMAN: I think he had two diseases, a minimal degree of portal cirrhosis and tumor formation in the liver, which was the main cause of his difficulty.

DR. CASTLEMAN: Dr. Point, you tried to "hit" this tumor with a needle?

DR. WARREN POINT: I saw this patient on the first admission. At that time I put the needle into the liver three times, and, as happens once or twice a year, I got tissue insufficient for diagnosis. Whenever I cannot obtain enough tissue for diagnosis, that means to me that there is a great deal of scar tissue and that the liver is very cirrhotic. The slide of the tissue suggested to me that the streaks of fibrosis and liver cells were the changes of cirrhosis although the amount of tissue was insufficient for me to be absolutely certain about the diagnosis. When the patient was readmitted to the hospital Dr. John Benson thought that this was something more than chronic cirrhosis. At that time it seemed more reasonable to do a peritoneoscopy, which unfortunately did not give us the diagnosis either because Dr. Benedict apparently obtained tissue from a regenerating lobule. With either a needle biopsy or a peritoneoscopic biopsy normal tissue may be removed; I suspect that it would be less likely to happen with a needle biopsy because of the thickness of tissue obtained through a needle. On a few occasions we have found normal liver tissue in a liver that was obviously cirrhotic. Is that not true?

DR. CASTLEMAN: Yes; especially if the cirrhosis is of the postnecrotic type in which the nodules vary in size; microscopical examination of tissue from an island of regeneration shows normal liver cells. These cells may not be in the normal arrangement of the liver lobule, but it is hazardous in a small piece to try to interpret the arrangement of cells. There may also be some fibrosis, but if the piece included the capsule, the fibrosis might just be the capsule of the liver. We reported in this particular case that we could not rule out cirrhosis but that we saw primarily normal liver cells. For that reason if one goes deeper into the liver with the needle there is perhaps a better chance of getting more than one particular lobule.

DR. BENEDICT: On some occasions I have not only taken a bite with the peritoneoscopy forceps, with which one may only get the capsule, which is often very tough, but sometimes I have combined that with a needle biopsy under direct vision. I think I probably should have done that in this patient, although I had no doubt at all when I looked at this liver that I was dealing with cirrhosis. Do we ever see hobnailing grossly when there is not cirrhosis?

DR. CASTLEMAN: That all depends on what you mean by hobnail. When we speak of hobnail livers we think primarily of the alcoholic or Laënnec cirrhosis, which produces nodules of uniform size, usually 2 or 3 mm. in diameter. If the nodules vary in size, we would not call the liver hobnail. Do you remember, Dr. Benedict, whether they were uniform or varied in size?

DR. BENEDICT: I should say that they were of varying sizes and all colors of the rainbow — a very irregular surface.

CLINICAL DIAGNOSES

Cirrhosis, ?postnecrotic, ?Laënnec's type.
?Portal-vein thrombosis.
?Hepatoma.

DR. EARLE M. CHAPMAN'S DIAGNOSES

Portal cirrhosis.
Malignant lymphoma, with spread throughout liver.

ANATOMICAL DIAGNOSES

Hepatoma, with tumor thrombosis of portal vein and metastasis to esophagus.
Portal cirrhosis, postnecrotic type.
Occlusion of superior mesenteric vein.
Early venous infarction of small and large bowel.
Splenomegaly, fibrocongestive.
Ascites.
Jaundice.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy we found 3 liters of fluid and a nodular liver. Dr. Benedict, would you call that hobnail (Fig. 1)?

DR. BENEDICT: I probably should in some of those areas of relatively uniformly sized nodules, but I should like to add that because of the varying sizes of the nodules and the multicolored appearance of the liver surface we considered superimposed hepatoma likely. We did not think lymphoma at all probable. Primary carcinoma of the liver, or hepatoma,

usually starts in a cirrhotic liver, but I do not recall ever having seen lymphoma of the liver superimposed on cirrhosis. Have you, Dr. Castleman?

DR. CASTLEMAN: I cannot recall such a case either.

I should not call this liver hobnail, because there were very large nodules interspersed with little ones and they were of various colors. There was a great deal of fibrosis. Certainly, that would make it difficult for Dr. Point to get any tissue, other than scar tissue. Externally, the liver nodules all seemed to be regenerating liver, but when we cut across this liver (Fig. 2), we found a large, irregular tumor that in many places was green. Whenever a tumor in the liver is green, it is very likely to be a primary hepatoma — that is, the liver cells composing the tumor are secreting bile. This hepatoma developed on a pre-existing, postnecrotic type of cirrhosis. These tumors are prone to invade the veins. This one extended the entire length of the portal vein and into the intrahepatic portal-vein radicles but stopped short at the junction of the splenic and superior mesenteric orifices. Apparently, it blocked the mesenteric vein because the entire bowel, especially the large bowel, was very red and almost gangrenous (Fig. 2). Microscopical section of bowel revealed markedly hemorrhagic involvement of the mucosa that was primarily due to the marked hypertension in the venous circuit — almost a venous infarction of the bowel produced by obliteration of the portal vein by the tumor.

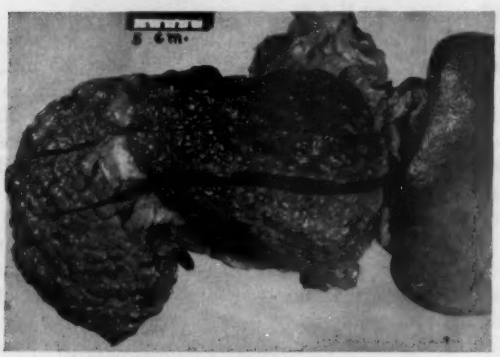


FIGURE 1.

DR. JOHN BENSON: How old was that necrosis in the bowel?

DR. CASTLEMAN: I cannot tell. When there is mesenteric venous thrombosis, the bowel may have this appearance even after two or three weeks' occlusion. The mucosa and the submucosa are the first to be involved; the necrosis can remain in the mucosa for a long period before it involves the muscularis.

The spleen weighed 750 gm. and was of the type that we see with portal cirrhosis of the liver. We examined the esophagus carefully but were not able to find many distended veins. However, a tiny vein in the esophageal mucosa contained hepatoma, so that the tumor had gone from the portal vein into the collateral and up into the esophageal vein — a finding that I have never seen before.

A PHYSICIAN: What did the bone marrow look like?

DR. CASTLEMAN: The marrow showed a preponderance of normoblasts. There was some red-cell hyperplasia such as is often seen in patients with cirrhosis.

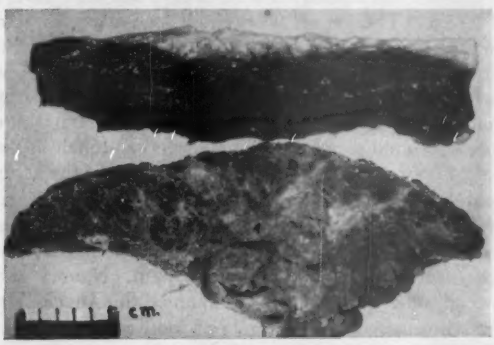


FIGURE 2. *Section of the Markedly Congested Large Bowel (Upper Specimen) and Cross-Section of the Cirrhotic Liver, Showing Tumor Extending into the Portal Vein (Lower Specimen).*

DR. POINT: I should like to comment on the cholinesterase. In the experience in this hospital the cholinesterase has not been a diagnostic procedure for neoplastic disease. At times we have seen values as low as this with liver failure as the result of cirrhosis or acute hepatitis. This man had progressive disease, as Dr. Chapman pointed out, and the cholinesterase did show it better than the other tests. Dr. Benson and the house staff suspected that the patient probably had a hepatoma. It was unfortunate that we could not prove it for them by tissue studies.

REFERENCES

1. Molander, D. W., Friedman, M. M., and LaDue, J. S. Serum cholinesterase in hepatic and neoplastic diseases: preliminary report. *Ann. Int. Med.* **41**:1139-1151, 1954.
2. McDermott, W. V., Jr., and Adams, R. D. Episodic stupor associated with Eck fistula in human with particular reference to metabolism of ammonia. *J. Clin. Investigation* **33**:1-9, 1954.

CASE 41132

PRESENTATION OF CASE

A fifty-four-year-old cleaning woman entered the hospital because of severe right-upper-quadrant pain.

She was in good health, except for occasional bouts of "indigestion" during the past fifteen or twenty years; these consisted of five-minute episodes of

"strong, smothering" epigastric distress, which developed at any time, was not related to food intake or posture and apparently was relieved by warm water and sodium bicarbonate. For about two months she had noted constipation relieved by occasional laxatives. Three weeks before admission a sudden, severe, knifelike right-upper-quadrant pain, unlike any previous distress, developed and radiated toward the right lower quadrant, but not to the scapula or back; however, an accompanying "funny, smothering" discomfort was noted in the small of the back. She had eaten some ice cream ten or fifteen minutes before the onset of the pain, which lasted for four or five hours and was associated with nausea and six episodes of emesis. The vomitus contained food particles. On awakening after an uneventful night, she vomited bitter, dark-brown material. During the next few days she felt "gassy" and belched more frequently than usual; the acute pain had subsided, but there was a residual soreness and tenderness to touch in the right upper quadrant. On the fifth day after the acute episode she returned to work and felt quite well thereafter, until ten days before admission, when she was awakened from sleep at 3 a.m. with a similar, but less severe, right-upper-quadrant pain. Nausea and two episodes of vomiting accompanied this attack. The first vomitus consisted largely of food consumed during the previous evening; the second vomitus was a bitter, brownish material. This pain lasted for three hours and was followed by right-upper-quadrant tenderness, which persisted until the time of admission. Five days before admission, when she was seen in the medical clinic, the right upper quadrant was noted to be tender. The area of liver dullness extended 8 cm. below the right costal margin and in the middle of the liver edge a tender mass, 3 by 2 cm., was felt. No specific therapy was given, and she was referred to the hospital.

The patient denied chills, fever, jaundice, dark urine, pruritus, change in caliber or color of stools, hematemesis and melena. Her appetite was good, and her weight had remained constant at about 178 pounds. No food intolerance was elicited, but she alleged a distaste for milk. No respiratory, cardiac or genitourinary symptoms were elicited. Thirty years before admission, she had had syphilis, which was treated at that time and again eighteen years before admission with arsenicals, bismuth, mercury and potassium iodide. The blood Hinton test was positive eighteen years before admission but became negative a year later and was still negative eleven years before admission; however, a Hinton test performed on blood drawn at the time of the current clinic visit was positive. She had had a gumma of the right leg twenty-nine years and a questionable gummatous leg ulcer eighteen years previously. No penicillin treatment had ever been given. She had five children.

Physical examination showed a moderately obese woman who appeared to be in good health. Areas of depigmentation were noted on both forearms and the dorsa of the hands. A healed ulcer scar was found on the left thigh. Examination of the head and neck was negative. The chest was clear. The heart border extended to the left midclavicular line and was otherwise normal. In the abdomen, the liver edge was indistinctly felt 7 cm. below the right costal margin; the liver was not tender. Below this, in the right pararectus position, a firm, rounded, tubular, tender mass, 5 cm. in diameter, was felt. It was freely movable, was questionably attached to the liver and moved slightly with respiration. Right-upper-quadrant tenderness was localized to this mass. No rebound tenderness or spasm was found. Pelvic examination revealed a relaxed perineum, with a minimal rectocele and cystocele; the cervix showed minimal erosions. Rectal examination was negative except for external hemorrhoids. Marked varicosities with partial thrombosis of the superficial veins were found in both lower extremities. Neurologic examination was negative.

The temperature was 98.8°F., the pulse 72, and the respirations 24. The blood pressure was 150 systolic, 95 diastolic.

Urinalysis on a voided specimen showed a trace of albumin and 50 to 100 white cells per high-power field with many clumps in the sediment. Examination of the blood revealed a hemoglobin of 14.8 gm. per 100 cc. and a white-cell count of 7700 with a normal differential. A brown stool specimen was guaiac negative. The fasting blood sugar was 107 mg., the nonprotein nitrogen 19 mg., the total bilirubin 0.5 mg., the total protein 7.0 gm., and the alkaline phosphatase 3.2 units per 100 cc.; the prothrombin time was 50 per cent of normal, and the cephalin flocculation was negative in forty-eight hours. A urine culture yielded rare coliform bacilli. An electrocardiographic tracing was borderline normal.

On attempted cholecystogram the gall bladder was not visualized. A globular mass was seen in the right midportion of the abdomen, and the lower pole of the right kidney could be seen through the upper portion of this mass (Fig. 1). Barium-enema examination gave no evidence of obstruction, diverticulum, ulceration or neoplasm; however, on the upper side of the transverse colon near the hepatic flexure, a mass 8 cm. wide appeared to press down on the large bowel (Fig. 2). The mass extended up to the liver and seemed to be extrinsic to the bowel. An x-ray film of the chest disclosed clear lung fields, a heart that was not enlarged and a tortuous aorta. An intravenous pyelogram revealed a normal urinary system. Again, a pyriform mass of soft-tissue density was seen to extend from the right upper quadrant to the right lower quadrant. Spot films in this area showed no stones, but several spots scattered throughout the pyriform shadow were thought to represent calcifications in the wall of a hugely distended gall bladder. On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. William C. Quinby, Jr.*: The chief question that concerns me today is, What was the mass? There were different descriptions of it by the radiologist so that I think we should see the films.

Dr. Joseph Hanelin: There were also different descriptions by the clinicians; it was described as both spherical and tubular.

The chest examination is negative. The preliminary pyelographic film shows a mass in the right side of the abdomen that partially overshadows the ileum. In a number of the films the mass appears to be almost spherical; yet in other projections there is a suggestion that it is globular (Fig. 1), with a relatively narrow upward extension. It may be that the mass rotates —that at one time it is seen on end and appears relatively rounded and at other times it is shown in its true length. The pyelogram, aside from the obvious mass, seems quite normal; there is no obvious displacement of the kidneys. The barium-enema examination (Fig. 2) shows no intrinsic colonic lesion, but the mass appears definitely to be pressing on the proximal portion of the transverse colon although it probably is not adherent to the colon. I am not positive about the presence of calcification within the mass itself. Some of the density that was thought to be calcium, I think, was material in the large bowel, but in no film can I see the area completely devoid of any density over it.

Figure 1. *Spot Film, Showing a Large Globular Mass in the Right Side of the Abdomen Extending to below the Iliac Crest (arrows).*

Dr. Quinby: Do you think the spleen is enlarged?

Dr. Hanelin: No; I think the spleen is normal in size. The liver may be slightly larger than it should be.

Dr. Quinby: The next to last sentence of the protocol stated the impression that the calcifications were in the wall of a hugely distended gall bladder. I do not see how I can arrive at any other conclusion than that this was a hugely distended gall bladder. The clinical history is not absolutely characteristic. But if one asks patients about their symptoms early in the course of cholecystic disease, the report of a strong smothering sensation, as opposed to pain, is not outside the realm of answers usually given. Nor is it always true that mild cholecystic attacks must be associated with specific food — the cooked fats are particularly incriminated. It is somewhat unusual for the distress to be relieved by alkali, but that again may be included among the premonitory symptoms in some patients. This patient, three weeks before admission, had an acute episode, which again was not entirely characteristic of cholecystitis. The radiation of the pain to the right lower quadrant of the abdomen rather than to the familiar areas of the scapula, the shoulder or parts of the back is not classic, but this distribution certainly may occur. There is emphasis on the fact that she vomited food particles early in the emeses, followed by fluids of varying descriptions. With obstruction to the cystic duct and an acute episode of gall-bladder inflammation one often discovers by clinical history that the previous meal has not left the stomach even though a number of hours have elapsed between the meal and the onset of vomiting.

Figure 2. *Barium-Enema Examination, Showing Extrinsic Pressure on the Proximal Transverse Colon by the Right-Sided Abdominal Mass.*

This patient was better after four or five days and went back to work; in other words, three weeks before admission there was an acute episode, which sub-

*Assistant in surgery, Massachusetts General Hospital.

sided to such an extent that she was able to return to work. The attack was then repeated in milder form ten days before admission. This time it came on at 3 o'clock in the morning, which is quite characteristic of a cholecystic attack. For some unknown reason cholecystic attacks often occur in the early morning hours. When she went to the medical clinic five days before admission she did not present an acute emergency because she was not admitted to the hospital for five days.

In the medical clinic, in spite of the patient's moderate obesity, the physician was able to feel a mass, 3 by 2 cm., in what appeared to be enlarged liver. That is not a very large mass to feel through an obese abdomen, so that I suggest it was larger than that. When she entered the hospital the clinical and x-ray descriptions of the mass indicate that it had increased rapidly in size since the outpatient visit. I do not see any way to eliminate a presumptive diagnosis of hydrops of the gall bladder. By hydrops, I do not mean necessarily that the fluid in the gall bladder was sterile. There may have been extensive empyema of the gall bladder, without very virulent organisms. Hydrops is certainly the clinical diagnosis to which the protocol leads one.

There is a problem here about the disease of syphilis. The patient demonstrated at the age of twenty-five the ability to form a gumma. I have to take that at its face value, as being a tertiary gummatous lesion. In spite of antisyphilitic therapy, she came back again at the age of about thirty-six with a lesion that was also thought to be a gumma. She responded to the antisyphilitic therapy at that time, and the serologic test remained negative for six years. The disease had apparently recrudesced, because on admission eleven years later the test was positive. In short she demonstrated an ability to form tertiary lesions of syphilis. Since there was an enlarged liver and a mass in the right upper quadrant attached to the liver, one should not forget that syphilis can imitate even hydrops of the gall bladder. However, I think it would be extremely unusual for a single gumma to have reached this size without causing something else to be palpable in the liver. The "hepar lobatum" of tertiary syphilis is a multilobulated liver. Customarily, the secondary lesion — the hepatitis of syphilis — is accompanied by far more dramatic changes in the tests of liver function than were shown here. And an enlarged spleen may occur with either type. The patient had hemorrhoids and varicose veins, which might be interpreted as venous obstruction secondary to syphilitic cirrhosis, I suppose, but the evidence for a single large gumma in the liver is too slim to draw me away from the other diagnosis.

There are other things that may have caused this mass. I think the urinary tract is clearly eliminated. Cysts of the upper pole of the kidneys and indeed of any part of the kidney can enlarge and present as masses in this region. I do not believe that disease of the pancreas could have reached this proportion or developed at this rate of speed without a far more dramatic course than this patient had.

Could the liver itself have been in this position? Was there a tumor or a deformity of the liver? In my readings for the discussion this morning, I was fascinated by the description of Riedel's lobe of the liver, which was described by him in 1888 and, indeed, before him. This "lobe" is a tonguelike projection of the liver often from the left lobe but, when on the right, usually fairly close to the gall bladder. Riedel believed that this "lobe" was due to disease of the gall bladder, but others have thought it was the result of adhesions (possibly secondary to cholecystic disease) between the liver and portions of the colon or other organs that attenuate and draw down a tongue of liver tissue. Occasionally, these lobes strangulate and present the symptoms of infarcted viscus or infarcted solid organ. If that had happened this patient would not have had two episodes separated by a symptom-free period but would have been forced into the hospital a great deal sooner. Furthermore, Dr. Hanelin has told me this mass was not firmly attached to the colon. Metastatic tumors I think I can discard. Her general welfare and history were too tenuous for that.

In reconstructing the illness I think that for a number of years she had malfunction of the gall bladder, giving mild symptoms of indigestion that were not entirely characteristic; that cholecystitis, with or without cholelithiasis, had produced a narrowing and partial obstruction of the cystic duct; that the episode three weeks before entry represented the beginning of a sealing off of the cystic duct; and that the mass, which rapidly progressed to the size seen in the x-ray films, was empyema of the gall bladder. The sealing off of the cystic duct eliminated any chance of visualizing dye in the gall bladder in the cholecystogram. The contents of the gall bladder gradually became thinner and more mucoid. I looked very carefully for evidence of calcium excretion into the gall bladder, which occurs when a cystic duct is occluded, but found none. I am left with the conclusion that the patient had cholecystitis, possibly with a small stone but not with a number of large ones, and that the ultimate diagnosis was hydrops of the gall bladder or a large empyema of mildly pathogenic bacteria.

Clinical Diagnoses

?Large cholelith, with possible obstruction of gall bladder neck.
?Carcinoma of gall bladder.
Late syphilis.
Urinary-tract infection.
Varicose veins and partial superficial phlebitis.

Dr. William C. Quinby's Diagnoses

Hydrops of gall bladder.
?Empyema of gall bladder.
Cholecystitis, probably with small stone.

Anatomical Diagnoses

Acute and chronic cholecystitis, with cholelithiasis.
Hydrops of gall bladder.
Adenocarcinoma of gall-bladder wall.

Pathological Discussion

Dr. Austin L. Vickery: The signs that you were being guided by in the protocol were bona fide, Dr. Quinby, leading to the correct diagnosis despite the red herrings of syphilis and other factors. Preoperatively, the surgeons thought that the patient probably had a large gall bladder with an acute inflammatory episode. At operation the gall bladder was found to be hugely distended, fully as large as that outlined in these x-ray films, inflamed and very tense. It was removed. At the time of the procedure the cystic duct appeared to be fibrotic and stenosed, agreeing with Dr. Quinby's concept that the gall-bladder enlargement was due to the accumulation of fluid, with a partially stenotic or completely obliterated cystic duct. The gall bladder measured 18.5 cm. in length and showed acute inflammation on the serosal surface and diffuse scarring of the wall. It was filled with brownish, thick bile and contained three gallstones; the contents were not those of an empyema. There were a few granular areas on the thickened and inflamed mucosa, and on microscopical examination in one area where there was merely focal thickening of the wall an adenocarcinoma was discovered. There was neither an associated mucosal nor an intraluminal mass. This is frequently observed with carcinomas of the gall bladder and is probably related to the rare preoperative diagnosis by usual x-ray technics. The carcinoma did not extend through the wall so almost certainly it has not spread by direct penetration into the liver bed or associated structures. The tumor in the gall bladder must be considered incidental to the primary disease — namely, recurrent bouts of cholecystitis, which almost certainly produced all the symptoms and was responsible for the eventual enlargement of the gall bladder.

A few years ago Arminski[1] reviewed the literature on carcinoma of the gall bladder. About 4.5 per cent of all forms found at autopsy proved to be primary in the gall bladder. About 50 per cent of a collected series of patients gave a history of old gall-bladder disease. Seventy-three per cent of 2100 patients with carcinoma of the gall bladder had associated cholelithiasis, and many authors consider the coexistence of gall-bladder disease and development of the carcinoma even higher than these figures indicate. Of course, this brings up the often-discussed subject of whether or not persons who have gallstones should have cholecystectomy to prevent the development of carcinoma of the gall bladder. Figures from the Mayo Clinic[2] have shown the rising (Table 1) frequency of gallstones at autopsy in females according to age groups, and make it obvious that if one were to remove every gall bladder that contained a calculus from female patients in the cancer age group one would have to operate on a good portion of the population. According to Arminski, it is certainly fair to say that carcinoma develops in only a small percentage of all patients with cholelithiasis. In any event there is a greater likelihood of the development of the complications of cholelithiasis that present surgical problems than the development of carcinoma.

Table 1. *Frequency of Gallstones in Women at the Mayo Clinic from 16,936 Autopsies.*

Decade	Percentage of Autopsies
5th	22.3
6th	30.7
7th	38.7
8th	46.7

Dr. Jacob C. Lerman: It is difficult to accept the figure of 4.5 per cent as the true frequency of carcinoma of the gall bladder.

Dr. Vickery: That 4.5 per cent related to all carcinomas — the rate of all carcinomas at autopsy that were primary in the gall bladder.

Dr. Lerman: It does seem a very difficult figure to accept. Carcinoma of the gall bladder is not very common.

Dr. Vickery: It is not common, and yet only last week I saw a patient in the operating room who was being operated on with a presumptive diagnosis of carcinoma of the head of the pancreas because of symptoms of painless jaundice and recurrent attacks of vague epigastric distress over a period of months. She had a carcinoma of the gall bladder. Warren and Balch[3] reviewed all the cases in this hospital from 1896 to 1936 and found 30 cases of gall-bladder carcinoma in 8000 autopsies — literally less than 1 a year in the postmortem population. However, 57 cases of gall-bladder carcinoma were found at operation in the Massachusetts General Hospital from 1933 to 1952.

References

1. Arminski, T. C. Primary carcinoma of gallbladder: collective review with addition of 25 cases from Grace Hospital, Detroit, Michigan. *Cancer* **2**:379-398, 1949.
2. Robertson, H. E., and Dochat, G. R. Pregnancy and gallstones: collective review. *Internat. Abstr. Surg.* **78**:193-204, 1944.
3. Warren, R., and Balch, F. G., Jr. Carcinoma of gall bladder: etiological role of gallstones. *Surgery* **7**:657-666, 1940.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Richard E. Alt, M.D.
Oliver Cope, M.D. — James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Robert M. Green, M.D. — J. Englebert Dunphy, M.D.
Dwight O'Hara, M.D. — Robert W. Buck, M.D.
Fletcher H. Colby, M.D. — Herrman L. Blumgart, M.D.
Robert L. Goodale, M.D. — Frank N. Allan, M.D.
Chester M. Jones, M.D. — Harvey A. Kelly, M.D.
Harvey R. Morrison, M.D. — Langdon Parsons, M.D.
Maxwell Finland, M.D. — Mark Aisner, M.D.
Vernon P. Williams, M.D. — Walter F. Lever, M.D.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (first-year interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal.

PROTEIN FOUNDATION AND RESEARCH ON BLOOD

THE development of the technics of blood fractionation by the late Dr. Edwin J. Cohn and his associates at Harvard has over the past twelve years brought about a revolution in knowledge of blood and in its application to the treatment and prevention of disease. But, although the accomplishments are already impressive, the developments that are only now emerging suggest the existence of many further important possibilities. Numerous institutions, in this country and abroad, are engaged in the exploration of these possibilities. In this process a role of central importance must be credited to Protein Foundation, Incorporated, a private nonprofit organization with headquarters in Cambridge.

The philosophy that was the starting point of this research was born to Dr. Cohn out of the emergency of World War II. There was a moral responsibility to the donor and to the nation, said this philosophy, to practice the greatest scientific economy in the administration of blood. The use of whole blood in conditions that could be managed with a single specific fraction represented a waste of precious materials. The task of science, therefore, was to break blood down into its constituent parts, to discover the special role played in the chemistry of the body by each part, to determine optimal conditions for its preservation and sterilization, to assess its therapeutic possibilities and, finally, to use for each specific condition only the fraction or combination of fractions found to be beneficial. Another vital aspect of this philosophy was the concept that it was the moral duty of scientists to protect the public by establishing qualitative standards for the production and testing of therapeutic products developed by their research.

Protein Foundation was originally set up for the primary function of administering, in the public interest and without royalty, the patents on discoveries made by Dr. Cohn and his associates at Harvard. It now includes, as an integral part of its organization, the Commission on Plasma Fractionation and Related Processes, which since 1944 has been responsible for assuring the maintenance of qualitative standards in the production of therapeutic blood derivatives developed by the Department of Physical Chemistry (later the University Laboratory of Physical Chemistry Related to Medicine and Public Health). In addition, the Foundation has undertaken the sponsorship of a program of research into the field of blood proteins and related tissues and, in particular, the practical application of such knowledge to clinical medicine and public health.

The systematic fractionation of plasma has by now resulted in the identification of more than 70 distinct protein constituents. Among the therapeutic weapons that have emerged from this research are serum albumin, widely used for the emergency treatment of shock and for the management of hypoproteinemia;

gamma globulin, for the prophylaxis of measles, infectious hepatitis and poliomyelitis; and antihemophilic globulin, fibrinogen and fibrin foam with thrombin, for the treatment of certain hemorrhagic disorders and for local hemostasis. The conclusive demonstration that very large pools of plasma, comprising several thousand bleedings (highly desirable to assure uniform products and economy of processing and control), could be processed to albumin and gamma globulin without the risk of transmission of homologous serum hepatitis, which has proved such a serious problem in the use of pooled plasma, has been one of the most important practical results of the plasma fractionation program. In addition, biochemical and physiologic research has been greatly stimulated by the availability of purified proteins for the investigation of biologic processes.

The work on the formed elements has also resulted in important advances. By means of new principles of separation, based on a unique method of centrifugation invented by Dr. Cohn and embodied in the ADL-Cohn blood fractionating machine, it has been possible to preserve platelets — until recently considered too labile for preservation — for periods of six months and more. Initial clinical experience indicates that their use may be of critical importance in the treatment of secondary thrombopenic purpura. Laboratory technics for the long-term preservation of erythrocytes by freezing in glycerol (developed by a group of British investigators and being studied with Dr. Ivan Brown, of Duke University) have been simplified and rendered practicable by variations in the ADL-Cohn fractionator that permit the rapid deglycerolization of the erythrocytes at the point of use.

Among the many studies being pursued by Protein Foundation scientists and by research scientists and clinicians in co-operating institutions are the relation of the lipoproteins to atherosclerosis and their role in the transport of steroid hormones; the possible use of iron-binding protein in the treatment of shock; the isolation of the various protein components of the clotting mechanism, to develop more satisfactory preparations for the study and treatment of hemorrhagic disorders; the ability of serum esterase to counteract the effects of certain anesthetics; the role of ceruloplasmin in Wilson's disease; and the chemical nature of recently localized protein factors that greatly accelerate phagocytosis by the leukocytes.

The development of the ADL-Cohn blood fractionator opens up extensive vistas in the fields of chemical and medical research and medical therapy. (The Arthur D. Little Company of Cambridge, which cooperated in the engineering of the machine, is now producing it in limited quantities for distribution to qualified research centers.) This remarkable apparatus is unique in providing a continuous *closed mechanical system* for taking blood from the human body, breaking it down into a series of fractions (erythrocytes, platelets, gamma globulin and stable plasma protein solution) and packaging the fractions in sterile plastic containers, ready for use or storage; the process is also applicable to the separation of leukocytes but this work is still in the experimental stages. Variations in design at present being engineered are expected to make possible the further fractionation of plasma within the machine. The great advantage of this procedure, both to research and to therapy, lies in its ability to provide blood derivatives that have been separated so rapidly and with so little trauma that they approximate their true state in nature.

The potential applications of the machine are manifold. One especially promising possibility lies in the technic of immunophoresis, as suggested by Dr. Joseph Stokes, Jr., of the University of Pennsylvania. This involves the repeated bleeding of donors who are convalescing from certain diseases or who have been hyperimmunized to them and whose gamma globulins therefore contain high titers of the corresponding antibodies. When ordinary procedures are employed, donors can be bled only once a month. But separation of the gamma globulin from the blood in the machine and return of cells and the remaining plasma proteins to the donor should make it possible to bleed individual donors as often as once a week, thus facilitating an adequate harvest of gamma globulins that are hyperimmune for specific conditions. It has been estimated that 3000 hyperimmune donors, bled once a week by this technic, would provide gamma globulin equivalent in prophylactic potential to the gamma globulin obtainable from 5,000,000 bleedings of normal donors.

It is certainly rare for a nonprofit organization that is not academic, governmental or industrially sponsored to be engaged in developmental research. But there is obviously a need for a common meeting ground between basic research groups in universities and hospitals and the pharmaceutical laboratories that must be the ultimate producers of their discoveries. It is the hope of the Protein Foundation that, as a private group positioned somewhere between basic science and industry and working in intimate contact with both, it will be able to expedite the process of development. And, by continuing the series of national conferences on blood that began at Harvard under the auspices of the National Research Council, the National Institutes of Health and the American Red Cross, it hopes, in addition, to facilitate the exchange of information and collaboration among the many groups across the country — academic, clinical, industrial and governmental — concerned with various aspects of research on blood.

It is encouraging to learn that the Harvard Corporation has made the facilities of the Blood Characterization and Preservation Laboratory at the Bussey Institute (next to the Biologic Laboratories of the State Department of Public Health at Forest Hills) available to Protein Foundation for its continuing developmental effort. The medical profession will watch with interest and sympathy the further unfolding of this significant program.

MEDICAL TASK FORCE REPORT

THE report of the "Medical Task Force" of the Hoover Commission on Organization of the Executive Branch of the Government was sent to Congress on February 28; it was almost immediately summarized in a special report from the Washington office of the American Medical Association. The more important recommendations of the report are certain to meet with approval from those interested in a more efficient and economical administration of the now appallingly widespread and costly medical programs of the nation. How they will fare politically is another matter; it is easier to go with the current of extravagant paternalism than to attempt to stem it.

In an effort first to find the facts of life that must be faced the task force determined the expenses of the United States for medical programs and compensation to total $4,100,000,000 a year. For this tidy sum the Government supplies whole or part medical care for 30,000,000 persons, a service that must be a source of considerable satisfaction to the proponents of so-called socialized medicine.

By way of lopping some of the superfluous growth from this luxuriant plant the report recommends, first, the establishment of a federal health council; second, the provision of *contributory* health insurance for military dependents and for personnel of the Coast Guard, the Public Health Service and the Coast and Geodetic Survey, and for dependents of the latter 3 groups; third, the regionalization of military medical services, with one service responsible for each region; fourth, the tightening up of ability-to-pay requirements in the Veterans Administration, and the codification of Veterans Administration laws and regulations; fifth, the virtual elimination of the present Public Health Service hospital and medical-care program.

Incorporated in these recommendations, mentioned here in the barest outline, are the elimination of the present medical-care program for merchant seamen, furnished by the Public Health Service at a cost of $14,000,000 in 1954 and considered no longer an obligation of the Government; the closing out of the Public Health Service general-hospital-care program at a saving of $19,000,000 a year and the closing of surplus Veterans Administration hospitals with the rescinding of present authorizations and appropriations for construction, except for those hospitals now building or under contract.

Other recommendations are that the present Armed Forces Medical Library be made into a "National Library of Medicine," under the supervision of the Smithsonian Institution and adequately financed and that the Hill–Burton hospital construction program be reappraised.

All in all, the proposals of the task force make so much sense in the curbing of waste and extravagance that a difficult time for them on Capitol Hill seems assured. It will be recalled that the main medical recommendation of the first Hoover Commission in 1949 for a united medical administration was discussed in Congress but was not adopted.

The proposals, however, as later reports revealed, were not wholly acceptable even to the Commission itself. The Secretary's letter from the American Medical Association, released a few days later than the report from the Washington office, announced that the Commission as a whole had rejected the so-called cut-off provision of the Medical Task Force relative to the time limit for the establishment of veterans' non-service-connected disability claims. By failing to accept the recommendation that such disabilities must be established within three years following discharge from active duty an estimated annual savings of $150,000,000 is set aside.

PATHOLOGISTS NEEDED

IN common with all aspects of science, pathology is suffering from a shortage of personnel. The rapid growth of the population, the ability to treat disease more satisfactorily by more detailed and quantitative study of the patient and the refinement of surgical diagnosis have all contributed to a much greater demand for pathologists than the current supply can fill. Although the American Board of Pathology has been certifying close to 200 additional pathologists annually, the need seems to be as great and as acute as ever. Recently, the United States Public Health Service sponsored a symposium to determine the causes of the shortage and to see what might be done to relieve it. Of course, one is at once faced with the problem that there are only so many medical graduates each year and that additional pathologists can be obtained only at the expense of medical workers in other fields.

Among the more interesting recommendations submitted by this symposium was one that the opportunities, economic and professional, that exist in the field be more widely publicized. Another was that there should be straight internships in pathology. It is recognized that if all medical students are forced to spend at least a year in another discipline before undertaking pathology, this will discourage some of those who otherwise might enter the field. Certain groups in the American Medical Association would abolish all internships in pathology. Fortunately, however, this avenue to training has not been closed.

A further problem has been that inadequate training has been given in experimental pathology in medical schools and, consequently, few medical students or postgraduate students have had an opportunity for realizing the potentials that exist in this specialty. The heart of the problem may well be that many qualified in pathology have been drawn into

hospital and private practice of pathology because of the large financial rewards, and that the departments of medical schools and the research positions have suffered in consequence.

TRAINING OF TECHNOLOGISTS

In its report, filed on January 19, 1955, to the General Court of Massachusetts, the Special Commission to Investigate the Training of Medical Laboratory Technologists (activated by Chapter 119 of the Resolves of 1954) recommends legislation to regulate and license schools for training of technologists, the schools to meet the standards of the American Medical Association's Council on Medical Education and Hospitals. The Commission submitted a bill to that effect.

When the Commission held its hearings, an impressive array of physicians, pathologists, hospital directors and other qualified persons testified to the fact that despite the vital importance to the physician, surgeon and pathologist of the medical technologist's varied and complicated activities there are in existence in Massachusetts schools with inadequate standards turning out incompetent and poorly trained personnel. It was stressed that anyone can start a school for training medical technologists at present and that the school can operate entirely without supervision or check on the quality of its work.

The witnesses outlined to the Commission the inherent dangers (obvious to the medical scientist) of work done by inadequately trained technologists, pointing out, too, that many of the technologists graduating from the unapproved schools are deficient not only in bacteriology, hematology and clinical chemistry but also in the whole field of clinical pathology. Some schools, it was disclosed, admit students direct from high school, some of them not even high-school graduates. The Commission decided as follows on the basis of evidence presented:

> . . . there is a great shortage of adequately trained medical technologists. To remedy the situation more students of high calibre must be attracted to the field. By raising the standards for entrance to the training schools better material which now avoids the field will be attracted. High school graduates alone are not sufficiently mature to enter it. College training with resultant additional maturity is requisite. The student should be protected against a poor school which takes his money for inadequate training which cannot assure him a position in a good hospital. The good schools do not cost the student as much as the poor ones. The $1000-a-year school costs the student more than two years at some college at $500 a year. In fact the year's training approved by the American Society of Clinical Pathologists at a good hospital school is free or at a nominal cost. There are many hospitals in this state which could, and should have such schools. The inferior schools should be made to comply with the standards set by the Council on Medical Education and Hospitals or cease to function.
>
> . . . The conclusion is inescapable that medical laboratory technologists, whose work is of prime importance in good medicine and good surgery, which can save thousands of human lives, should be adequately trained in schools which must meet the standards of the Council on Medical Education and Hospitals.

It should be pointed out that the legislation proposed by the Commission does not interfere with the hiring or discharging of laboratory personnel, nor does it set up a board of registration of medical technologists.

The American Society of Clinical Pathologists Board of Registry of Medical Technologists examines and registers applicants, who, to become qualified, must have the equivalent of two years of basic science in college (biology and chemistry required), in addition to a minimum of a year's training in a school approved by the Council on Medical Education and Hospitals of the American Medical Association, working closely with the Society of Clinical Pathologists, whose Board of Schools of Medical Technology evaluates and inspects individual schools.

The Society's registration of medical technologists amounts to recognition and evidence of adequate training and knowledge and competency, and its standards of registration are endorsed and accepted by the American Medical Association, the American College of Surgeons, the American Hospital Association and the Catholic Hospital Association.

The American Society of Medical Technologists (not to be confused with the unrecognized American Medical Technologists organization that has set up its own board of registration) accepts as members only those who have met the standards required for registration.

The bill presented to the General Court by the Commission offers another warranty of the competency of medical technologists, often referred to as the third hand of the pathologist. The Committee on State Legislation of the Massachusetts Medical Society has approved this bill.

Dr. W. T. Grant has retired from the assistant editorship of the Georgia Blister and Critic published at Atalanta, Geo.; Dr. H. Ramsay and two associate editors will hereafter conduct it.

Boston M. & S. J., *April 5, 1855*

MASSACHUSETTS MEDICAL SOCIETY

CIRCULAR OF ADVANCE INFORMATION

Copies of the *Circular of Advance Information for Councilors* for the May 16 meeting of the Council are available, as long as the supply lasts, to all fellows who apply to the Secretary, 22 Fenway, Boston.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

Orthopedic Clinic	Date	Clinic Consultant
Salem	April 4	Paul W. Hugenberger, M.D.
Gardner	April 5	Carter R. Rowe, M.D.
Haverhill	April 6	William T. Green, M.D.
Greenfield	April 7	Charles L. Sturdevant, M.D.
Lynn*	April 11	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Brockton	April 14	George W. Van Gorder, M.D.
Worcester	April 15	John W. O'Meara, M.D.
Pittsfield	April 20	Edward J. Coughlin, Jr., M.D.
Fall River	April 25	David S. Grice, M.D.
Springfield	April 26	James D. Fisher, M.D.
Hyannis	April 28	Paul L. Norton, M.D.

Rheumatic-Fever Clinic	Dates
North Reading	April 5, 12, 26
Fitchburg	April 6, 13, 20, 27

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

CORRESPONDENCE

IN REPLY TO "A DEFENSE OF SODIUM DEHYDROCHOLATE"

To the Editor: In answering Dr. R. L. Conklin's letter entitled "A Defense of Sodium Dehydrocholate," I shall make an attempt to explain our views on the subject.

When a member of the medical profession criticizes the basic concepts of the medical literature, the "youthful, undisciplined" research fellows and the *New England Journal of Medicine*, he must have given serious consideration to the implications involved. To reply to such a letter is difficult, for I feel it necessary to defend myself and my colleagues in a matter that I went over in great detail with Dr. Conklin when he visited Augusta after our paper was published. He had complete access to our records at that time. Is it not strange that over a year has passed since his visit and that the publishing of another paper from Boston should bring out such severe criticism now?

In his letter Dr. Conklin criticized Sanchez and Morris for having no part in treating the patients they described. Yet he is not above criticizing our treatment of a patient that he himself did not see or treat. Actually, the particular treatment involved in this patient is of little consequence because the temporal relation of the injection of Decholin and the response of the patient was clearly brought out in the paper — "It is of interest that the circulatory collapse was so severe and acute that the usual endpoint was not obtained." This temporal relation was what we attempted to make clear.

What type of censorship is suggested by Dr. Conklin? I believe that regardless of censorship at the local level, as he proposes, the editorial board of the *New England Journal of Medicine* is capable of deciding what should be published better than one who states that "unfavorable criticism of an established product in papers of this caliber is unfortunate and costly both to the manufacturer and to the clinician." Other drug companies whose products have been under criticism set out to correct the underlying defects and made a sincere effort to see that the medical profession was properly informed of the potential hazards. Would not this have been a better attitude and approach for Dr. Conklin and the Ames Laboratory than the severe criticism of those who are attempting to report on observations that are considered to be worthy of attention to the medical profession?

I hope this letter will in no way offend Dr. Conklin or his associates, but might he not heed the advice mentioned in his letter that "many physicians have advised our professional service representatives that they view with alarm the use of Decholin for determining circulation time"? To recognize that the case reports on difficulty with Decholin in the determination of circulation time have come from many areas of the country should emphasize the fact that potential hazards are possible, though uncommon, when Decholin is used.

Robert P. Coggins, M.D.
Senior Resident, Department of Medicine
Medical College of Georgia
Augusta, Georgia

To the Editor: Dr. Conklin's letter on sodium dehydrocholate appears to us to be inaccurate in certain details, but we are in entire agreement with his emphasis on the importance of a careful assessment of clinical facts and on the necessity of review and supervision of published reports of younger men by responsible heads of departments.

In this connection, and for Dr. Conklin's information, the events leading up to our report in the *New England Journal of Medicine* may be of some interest. This report was not undertaken quite so casually as he suggested namely, that "4 cases taken from the files of the record library" were reviewed. Actually, the occurrence of an alarming train of symptoms and death in Case 1 was widely discussed at our staff conferences and was the subject of a clinicopathological conference. After a second death in a few months under equally disturbing circumstances, it was suggested to me by the chief of the cardiac service at the Massachusetts General Hospital that a careful review of the literature and of the experience elsewhere in Boston be undertaken. As a result of this investigation, and with the full approval and supervision of the chiefs of the respective services at the Massachusetts General and Beth Israel hospitals, the sequence of events in the 4 cases was recorded. It was, and still is, our primary aim to call attention again to the well known fact that the intravenous injection of any foreign material, however "safe," involves an element of risk in patients seriously ill with congestive heart failure, and accidents occasionally occur. As emphasized in our report, the sodium dehydrocholate has provided one of the safest and probably most widely used methods for determining the circulation time. It is of value in an occasional case in which the information is helpful in diagnosis and treatment, but its "routine" use, especially in patients suspected of allergy, is to be deplored.

I hope that this exposition of the circumstances that inspired our report (of the details of which Dr. Conklin could have had no knowledge), as well as the practices employed in connection with the publication of reports from the two hospitals involved, will serve in some measure to reassure him that this study was not undertaken lightly or with any motive other than the welfare of patients.

Guillermo Sanchez, M.D.
Cardiac Laboratory
Massachusetts General Hospital
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Synopsis of Anaesthesia. By J. Alfred Lee, M.R.C.S., L.R.C.P., M.M.S.A., D.A., F.F.A.R.C.S., consultant anesthetist, Southend-on-Sea Hospital. Third edition. 12°, cloth, 483 pp., with 72 illustrations. Baltimore: Williams and Wilkins, 1953. $3.50.

This summary, first published in 1947, has been revised and brought up to date. The treatment is comprehensive

in scope, the whole field of anesthesia being covered. There is an extensive index; the printing was done in Great Britain, and the publishing is good. The book should prove valuable as a quick reference source.

Histopathology of the Skin. By Walter F. Lever, M.D., clinical associate in dermatology, Harvard Medical School, assistant dermatologist, Massachusetts General Hospital, associate in dermatology, Peter Bent Brigham Hospital, and consulting dermatologist, Massachusetts Eye and Ear Infirmary, Children's Hospital and Robert Breck Brigham Hospital. Second edition. 8°, cloth, 518 pp., with 281 illustrations, with 8 in color. Philadelphia: J. B. Lippincott Company, 1954. $12.00.

This new edition of a standard special book has been revised, and new material has been incorporated throughout the text. The descriptions of the vesicular and bulbous diseases have been completely rewritten and grouped in a new chapter. Discussion of the following diseases has been added: beryllium granuloma, papular myxedema, porphyria, ochronosis, hibernoma and hemangiopericytoma. Revised bibliographies are appended to the chapters; there is a glossary of terms and a good index. The book, which is well illustrated and well published, should be in all dermatologic collections.

The Hepatic Circulation and Portal Hypertension. By Charles G. Child, III, M.D., professor of surgery, Tufts College Medical School, chairman, Department of Surgery, New England Center Hospital, and, formerly, associate professor of clinical surgery, Cornell University Medical College, and attending surgeon, New York Hospital; from the Department of Surgery and the Laboratory of Surgical Research, New York Hospital-Cornell Medical Center, in collaboration with the staff. 8°, cloth, 444 pp., with 132 illustrations and 19 tables. Philadelphia: W. B. Saunders Company, 1954. $12.00.

Dr. Child and his collaborators have made a comprehensive study of the hepatic and collateral circulations in their physiologic and clinical aspects. The literature has been surveyed, and there is a bibliography of 46 pages. The appendixes include the results of work on monkeys and dogs, the effect of epinephrine on portal venous pressure in normal dogs, monkeys and men, and 36 case abstracts of portal hypertension. The publishing is excellent, and the book is recommended for all collections on the subject.

Auditory Disorders in Children: A manual for differential diagnosis. By Helmer R. Myklebust, professor of audiology, School of Speech, professor of otolaryngology, School of Medicine, and director, Children's Hearing and Aphasia Clinic, Northwestern University. 8°, cloth, 367 pp. New York: Grune and Stratton, 1954. $6.00.

This manual is written for all persons interested in auditory disorders of young children. The text is divided into five main parts as follows: professional specialization, history taking and interpretation, behavioral symptomatology, examination methods and procedures, and illustrative cases and recommendations for training. Under symptomatology auditory disorders due to peripheral deafness, psychic deafness and mental deficiency are discussed. The literature has been surveyed, and lists of references are appended to the chapters. There are indexes of authors and subjects.

Social Science in Medicine. By Leo W. Simmons, professor of sociology, Yale University; and Harold G. Wolff, professor of medicine (neurology), Cornell University Medical College. 8°, cloth, 254 pp. New York: Russell Sage Foundation, 1954. $3.50.

The authors, a physician and a sociologist, discuss the interrelations of medicine and social science. They have made a thorough study of the subject and stress the importance of studying the aspects of the patient's environment that affect his illness and recovery. There is a bibliography of 46 pages and a good index. The publishing is well done. The book is recommended for all medical libraries.

The Deaf and Their Problems: A study in special education. By Kenneth W. Hodgson, M.A. (Cantab.) With a preface by Sir Richard Paget, Bart., fellow of the Physical Society, etc. 8°, cloth, 364 pp. New York: Philosophical Library, Incorporated, 1954. $6.00.

This semipopular book discusses the general problems of deafness and the historical aspects of the subject from the ancient and medieval worlds to the twentieth century.

Experimental Diabetes and Its Relation to the Clinical Disease: A symposium organized by The Council for International Organizations of Medical Sciences. Established under the joint asupices of U.N.E.S.C.O. and W.H.O. Consulting editors: J. P. Hoet (Belgium); F. G. Young (U.K.). Editors for the Council: J. F. Delafresnaye, C.I.O.M.S., Paris, France; G. Howard Smith, Department of Biochemistry, Cambridge, England. 8°, cloth, 352 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $5.50.

Twenty authorities from all parts of the world, including six from the United States, participated in this symposium. Lists of references are appended to the papers, and there is a good index. The printing was done in Great Britain. The book should be in all collections on diabetes.

Manual of Proctology. By Emil Granet, M.D., lecturer, Graduate School, Columbia University, visiting surgeon (proctology), Sea View Hospital, and associate surgeon (proctology), French Hospital, New York, commander (MC), USNR. 8°, cloth, 346 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $7.50.

This manual has been written primarily for the general practitioner. The early chapters deal with anatomy, diagnosis and symptomatology, anesthesia, general therapy and pediatric proctology. These are followed by chapters on diseases of the anus and colon. There is a good index, and the small book is well published.

Anesthesiology. By forty American authors. Supervising editor, Donald E. Hale, head, Department of Anesthesiology, Cleveland Clinic, Cleveland, Ohio. 4°, cloth, 756 pp., with 149 illustrations. Philadelphia: F. A. Davis Company, 1954. $15.00.

This comprehensive treatise covers the whole field of anesthesia and related subjects. It presents the latest knowledge on the subject. Lists of references are appended to the chapters, and there is a good index. The text is printed in a two-column format; there is an extensive index. The book should be in all collections on the subject. The price is not excessive for this type of book.

Studies from The Rockefeller Institute for Medical Research. Reprints, volume 148. 8°, paper, 597 pp., with illustrations. New York, New York: Rockefeller Institute for Medical Research, 1954.

NOTICES

AMERICAN SOCIETY OF X-RAY TECHNICIANS

The annual convention of the American Society of X-Ray Technicians will be held at the Hotel Statler, Boston, May 29 through June 2.

Refresher courses will be of special interest, and information about them may be obtained from Marion Snyder, R.T., Registrar, 1165 West Water Street, Elmira, New York.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The annual meeting of the American College of Chest Physicians will be held at the Ambassador Hotel, Atlantic City, June 1-5.

All interested physicians are invited; there is no registration fee. Further information may be obtained from the

Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

AMERICAN ACADEMY OF DENTAL MEDICINE

The ninth annual meeting of the American Academy of Dental Medicine will be held at the Park Sheraton Hotel, New York City, May 13-15.

The main themes of the scientific sessions will concern the stress syndrome, mucous-membrane changes and implant dentures. Programs and reservations may be obtained from Dr. William M. Greenhut, 124 East 84th Street, New York 28, New York.

ALPHA OMEGA ALPHA LECTURE

The annual Alpha Omega Alpha lecture of the State University of New York College of Medicine at New York City will be delivered by Dr. Arthur J. Patek, Jr., Columbia University College of Physicians and Surgeons, on the topic "Laënnec's Cirrhosis: Present-day concepts in treatment," in Hoagland Hall, 335 Henry Street, Brooklyn, on Tuesday, April 26, at 5:15 p.m. All interested persons are invited.

INSTITUTO NACIONAL DE CARDIOLOGÍA DE MÉXICO

The Sociedad de Internos y Becarios del Instituto Nacional de Cardiología de México will present seminars on cardiology to commemorate its eleventh anniversary at the Institute, 300 Avenida Cuauhtemoc, Mexico City, from April 27 through 30.

SOCIETY MEETINGS AND CONFERENCES

March–April. Postgraduate Medical Institute. Page 451, issue of September 9.

March–May. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

April 1. American Psychiatric Association (Massachusetts District Branch). Page 289, issue of February 17.

April 1. New England Society of Anesthesiologists. Page 289, issue of February 17.

April 2–May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

April 4–18. Hartford Medical Society. Page 289, issue of February 17.

April 4–28. Consultation Clinics for Crippled Children in Massachusetts. Page 551.

April 5. Microcirculatory Conference. Page 289, issue of February 17.

April 5–May 26. Boston City Hospital. House Officers' Lectures. Page 509, issue of March 24.

April 6 and 7. American Heart Association. Page 371, issue of March 3.

April 6–May 25. Lahey Clinic Lectures. Page 461, issue of March 17.

April 6–June 15. Boston State Hospital. Psychiatry Seminars. Page 461, issue of March 17.

April 7–9. Postgraduate Course in Obstetrics and Pediatrics. Page 329, issue of February 24.

April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.

April 13. Chelsea Soldiers' Home. Page 329, issue of February 24.

April 13. New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.

April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.

April 23. Massachusetts State Society of Medical Technologists. Page 461, issue of March 17.

April 23–29. Industrial Health Conference. Page 509, issue of March 24.

April 25–30. American College of Allergists. Page 462, issue of March 17.

April 26. Harvard Medical Society. Page 509, issue of March 24.

April 26. Alpha Omega Alpha Lecture. Notice above.

April 27–30. Instituto Nacional de Cardiología de México. Notice above.

April 28–30. American Goiter Association. Page 329, issue of February 24.

April 30. State University College of Medicine at New York City. Page 289, issue of February 17.

April 30. Phi Delta Epsilon Fraternity. Graduate Club of Boston. Page 461, issue of March 17.

May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.

May 6–8. Student American Medical Association. Page 461, issue of March 17.

May 13 and 14. American Association for Cleft Palate Rehabilitation. Page 461, issue of March 17.

May 13–15. American Academy of Dental Medicine. Notice above.

May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 18–20. American College of Cardiology. Page 414, issue of March 10.

May 23–27. American Trudeau Society. Page 462, issue of March 17.

May 29–June 2. American Society of X-Ray Technicians. Page 553.

June 1–5. American College of Chest Physicians. Page 553.

June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

June 7–9. United States Public Health Service Medical-Officer Examinations. Page 509, issue of March 24.

June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

July, August and September. Beth Israel Hospital Course. Page 509, issue of March 24.

July 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.

July 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.

August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

October 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

November 29–December 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 7

THURSDAY, APRIL 7

American Heart Association. Northfield Hotel, East Northfield, Massachusetts.

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Thoracic Conference. Main Amphitheater. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*7:00 p.m. Boston City Hospital. House Officers' Association. The Genesis of Endometrial Carcinoma. Dr. Arthur T. Hertig. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

FRIDAY, APRIL 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, APRIL 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.

*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, APRIL 11

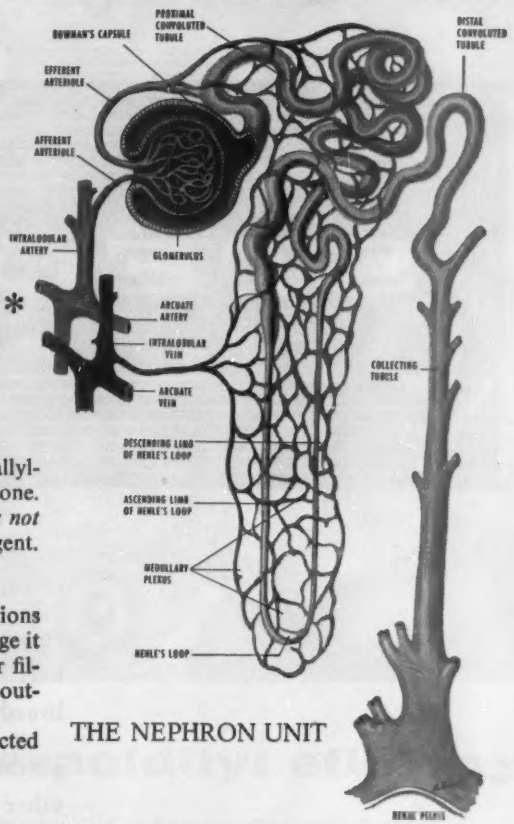
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

(Concluded on page xxii)

A NEW PRODUCT OF SEARLE RESEARCH

New, Effective, Non-Mercurial Oral Diuretic

MICTINE*



THE NEPHRON UNIT

STRUCTURE

Mictine, brand of aminometramide, is l-allyl-3-ethyl-6-aminotetrahydropyrimidinedione. Mictine—result of years of research—*is not* a mercurial, xanthine or sulfonamide agent.

ACTION AND EFFECTIVENESS

Mictine inhibits reabsorption of sodium ions by the renal tubule. In therapeutic dosage it has not caused any effect on glomerular filtration rate, renal plasma flow, cardiac output, heart rate or blood pressure.

Approximately 70 per cent of unselected edematous patients respond to Mictine.

TOLERANCE

Mictine is without serious toxic effects as used. It has not produced any alteration in the blood or blood-forming organs or in renal or hepatic function. At times headache or gastrointestinal symptoms (anorexia or nausea but rarely vomiting or diarrhea) have occurred, however, these effects may be reduced to a minimum by giving Mictine on an interrupted dosage schedule.

ADMINISTRATION

Mictine is useful primarily in the *maintenance* of an edema-free state and in the *initial and continuing* control of patients in mild congestive failure. In such patients, dosage is one to four tablets daily *with meals*, in divided doses on an interrupted schedule. An interrupted dosage schedule may be accomplished by giving the drug on alternate days; or by its administration for three consecutive days and its omission for four consecutive days.

Mictine also may be used for *initial* diuresis in *more severe* congestive states, particularly when mercurial diuretics are contraindicated. In these more severe congestive states, dosage is four to six tablets daily *with meals*, in divided doses on an interrupted schedule similar to those mentioned above.

SUPPLIED

Uncoated tablets of 200 mg. in bottles of 100.

*Trademark of G. D. Searle & Co.

SEARLE

broad spectrum antibiotic of choice

STECLIN

SQUIBB TETRACYCLINE

promptly reaches high levels in the urine

crosses the intact meningeal barrier more readily than the other broad spectrum antibiotics

produces higher blood levels than the other broad spectrum antibiotics

less gastrointestinal side effects than the other broad spectrum antibiotics

Minimum adult dose: **250 mg. q.i.d.**
250 mg. capsules, bottles of 16 and 100.
50 and 100 mg. capsules, bottles of 25 and 100.

SQUIBB

"STECLIN" IS A SQUIBB TRADEMARK

Gastric Hyperacidity: etiology

People being people, environmental factors contributory to gastric hyperacidity are hard to remove, even when their role is clearly defined. But, the physician has a sure, simple—even pleasant—way of relieving the acid distress caused by:

- dietary indiscretion
- nervous tension
- emotional stress
- food intolerances
- excessive smoking
- alcoholic beverages

Gelusil promptly and effectively controls the excessive gastric acidity of "heartburn" and chronic indigestion. And it affords equally rapid relief in peptic ulcer. Sustained action is assured by combining magnesium trisilicate with the specially prepared aluminum hydroxide gel.

Free from constipation: Gelusil's aluminum hydroxide component is specially prepared: the concentration of aluminum ions is accordingly low; hence the formation of astringent—and constipating—aluminum chloride is minimal.

Free from acid rebound: Unlike soluble alkalies, Gelusil does not over-neutralize or alkalinize. It maintains the gastric pH in a mildly acid range—that of maximum physiologic functioning.

Dosage—2 tablets or 2 teaspoonfuls two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel.

Available—Gelusil Tablets in packages of 50, 100, 1000 and 5000. Gelusil Liquid in bottles of 6 and 12 fluidounces.

Gelusil®

Antacid • Adsorbent

WARNER-CHILCOTT

Under Your Fracture and Dislocation Clause

You Get all the "Breaks"

Since emergency cash payments under the new Fracture and Dislocation Clause are not contingent upon loss of time and are made even though the insured may be performing all or part of his professional duties, substantial extra benefits are paid to policy owners.

A recent analysis of payments made in 36 fracture or dislocation cases shows

Benefits paid for..... 232 weeks

Actual time lost..... 59 weeks—6 days

Extra weeks of BENEFITS ACTUALLY PAID 172 weeks—1day

Policy owners have benefited in two ways — financially and through broader coverage for conditions ordinarily excluded under most policies. Obviously, any policy without this fracture and dislocation feature is of considerably less value.

This Clause is only one of many important features of the Plan designed exclusively for members of the Massachusetts Medical Society by Lester L. Burdick, Inc.

A postcard will bring full information concerning seven other advantages available exclusively to doctors under this Professional Disability Plan.

LB LESTER L. BURDICK, INC.

Loyalty Group Insurance

19 CONGRESS ST., BOSTON 9, MASS.

Phone Richmond 2-2740

When the mother asks—

"Which vitamin drops should I use?" --
she looks to you for <u>specific</u> advice.
And when you specify easy-to-take
Vi-Penta® Drops 'Roche,' you know
they are dated to ensure full
potency...they contain <u>synthetic</u>
vitamin A plus seven other vitamins
(including B_6)...and they taste good.

Especially
for pediatric
infections —

When you prescribe Gantrisin®(acetyl) Pediatric Suspension 'Roche,' you may be sure of two things: It really tastes good -- so good even sick children take it gladly -- and it offers wide-spectrum antibacterial therapy that is usually well tolerated.

You Are Cordially Invited
To Attend
The Formal Opening of

TWEEDS LTD
BOSTON

Clothing Imported Accessories

445 Brookline Avenue

(In the Heart of Boston's Medical Community)

Wednesday, April 6

10:30 A.M. — 5:30 P.M.

OPEN HOUSE REFRESHMENTS

Our Clothes Are Always Styled in
CONSERVATIVE GOOD TASTE

Suits from $65
Sport Coats from $45
Slacks from $16.50
Custom-made suits from $95

As Portrayed
by our
Chadwick
MODEL

- *Flexible construction
- *No excess padding or canvas stiffening
- *Pliable hand-tailoring
- *Natural shoulders
- *Easy lines

Our accessories and furnishings are carefully coordinated for just the right touch of quiet distinction!

Declaration of Purpose

I. Our Location:

We selected a location convenient to Boston's hospital center, since our purpose is to cater principally to the medical profession. Our shop is located at 445 Brookline Avenue.

II. Our Modus Operandi:

We will operate an intimate, casual, "no-pressure" men's shop serving the apparel needs of discriminating men.

III. Our Merchandise:

Our clothing will always be in "conservative good taste." A leading men's apparel stylist will always be available for advice and consultation.

IV. Our Objective:

Our goals are service, plus fine merchandise. In this way we hope to become recognized as apparel consultants for men seeking distinctive apparel!

V. Our Service:

Your new men's apparel shop will be open from 9 a.m. to 5:30 p.m. Appointments for selections and fittings will be made for your convenience at the store or at your office.

TWEEDS LTD
BOSTON

CLOTHING IMPORTED ACCESSORIES

445 Brookline Avenue

(In the Heart of Boston's Medical Center)

Dear Doctor:

The largest single item of savings in your 1954 tax filing may very well depend upon the utilization of competent professional tax accounting services.

We respectfully request your inquiry for successful case histories and names of professional people whose tax and accounting responsibilities we have satisfactorily handled.

◆

Arthur M. Agnew, President

FEDERATED ACCOUNTING SERVICES,

Inc.

116 Newbury Street
Boston 16, Massachusetts
COpley 7-5050

ELECTROENCEPHALOGRAPHIC LABORATORY, INC.
270 Commonwealth Ave., Boston KE 6-8100
Electroencephalograms
Electromyograms

PHYSICIAN'S Office FURNITURE. All standard lines, new. Used equipment from time to time. Convenient terms. Visit our showroom close by Veterans Hospital. Ample parking. T. J. NOONAN Co., 408 South Huntington Avenue, Jamaica Plain (Boston 30), Mass. Phone JAmaica 2-8700 for literature. Medical, hospital, laboratory, sickroom supplies. B260-20-tf

TWO MEDICAL RESIDENCIES, at the third year level, available July 1, 1955 in a four year AMA approved program leading to Board certification. Write: Executive Vice-President, The Roosevelt Hospital, 428 West 59th Street, New York 19, N. Y. B189-3-tf

RESIDENCIES AVAILABLE—Veterans Administration Hospital. Large southern medical center, affiliated with Tulane and Louisiana State University Schools of Medicine. Fully approved. Openings July 1, 1955 in Internal Medicine, General Surgery, Urology, Ophthalmology, Pathology and Psychiatry. Apply — Dr. W. W. Frye, Chairman, Deans Committee, 1542 Tulane Avenue, New Orleans, Louisiana. B194-5-13t

OPENING for 1 resident at the Gaston Hospital, Dallas, Texas. Approved by American Board for 1 year general surgery. Salary $200.00 per month and complete maintenance. B30-11-tf

FOR RENT — Newly renovated medical suite. Main thoroughfare. Call MAlden 2-2117 or address A199, *New Eng. J. Med.* 11-3t

WELLESLEY—Colonial home suitable for doctor. Fine condition, excellent location. WEllesley 5-4087. B205-9-13t

WANTED — PEDIATRICIAN OR INTERNIST — Graduate of approved medical school, internship and at least two years residency, active interest in research, at large State School for Mentally Retarded. Liberal schedule, excellent library service. 2½-hour drive to Boston. Near ocean and large lake. Good salary. Paid vacation, sick leave, outstanding retirement system. Man or woman. Apply Box C, Pownal, Maine. B218-12-3t

COLONIC IRRIGATIONS, massage, diathermy. Beatrice M. Woods, 511 Beacon Street, Boston, CO 6-8722. B80-16-tf

Worcester Medical Laboratory
COMPLETE SERVICE
for the physician
44 West Street Worcester, Mass.
PLeasant 2-3664
Under Medical Supervision—Inquiries Invited

BIND your *New England Journal of Medicine*. Make it a permanent part of your library—for easy reference and lasting wear. In full black library buckram, only $3.30 per volume, plus shipping charges. All other journals and periodicals bound also. Inquiries invited. Norden Bindery, 2100 West Grand Avenue, Chicago 12, Ill. B300-14-tf

UNITED LIMB & BRACE CO., Inc., manufacturers of artificial limbs. 61 Hanover Street, Boston, CA 7-2183. B517-6-tf

OFFICE FURNITURE—New—Used—Refinished. Bought and sold. Desk Clearing House, 115 Broad Street, Boston. HU 2-1318. B72-22-tf

DOCTOR'S SUITE ON FIRST FLOOR — Partly furnished if desired. Commonwealth Avenue near Dartmouth Street. KE 6-9230. B340-19-tf

STORROW HOUSE
(Former Storrow Estate at Lincoln, Mass.)
Staffed and Operated by the
MASSACHUSETTS GENERAL HOSPITAL
For nonpsychiatric ambulatory and semi-ambulatory patients needing rest or convalescent facilities.
CHARGES: $7.00 to $10.00 per day
Transportation for visits to physician's office provided. For information, call LIncoln 6-0343 or Massachusetts General Hospital Admitting Office LA 3-8200.

WANTED—RESIDENT PHYSICIAN —Position open July 1, 1955. Grand opportunity for young man who has just completed his internship or residency. General hospital, 142 beds and organized medical staff, 50 physicians. Applications accepted for 1 year or longer as individual desires. Starting salary $3,200 per annum. Desirable opening with close association with medical profession of community. Apply: Matthew I. Barron, Director, Portland City Hospital, Portland, Maine. Interview granted at applicant's convenience. B204-9-8t

NISSEN'S INSTITUTE OF PHYSICAL THERAPY, 1126 Boylston Street, Boston, KE 6-1030. Cape Cod office, Route 28, West Harwich. Telephone Harwich 984. B290-3-tf

GENERAL PRACTITIONER to take over office and practice of physician in Leominster, Mass. Leaving July 1 for specialty training. Will introduce. Address A200, *New Eng. J. Med.* 11-tf

(Advertisements continued on page xx)

For the Aged and Senile Patient

ORAL *Metrazol*

—to help the geriatric patient with early or advanced signs of mental confusion attain a more optimistic outlook on life, to be more cooperative and alert, often with improvement in appetite and sleep pattern.

Metrazol, a centrally acting stimulant, increases respiratory and circulatory efficiency without overexcitation or hypertensive effect.

Dose: 1½ to 3 grains, 1 or 2 teaspoonfuls Liquidum, or the tablets, every three or four hours.

Metrazol tablets, 1½ grs. (100 mg.) each. Metrazol Liquidum, a wine-like flavored 15 per cent alcoholic elixir containing 100 mg. Metrazol and 1 mg. thiamine HCl per teaspoonful.

Metrazol®, brand of pentylenetetrazol, a product of E. Bilhuber, Inc.

BILHUBER-KNOLL CORP. *distributor* ORANGE NEW JERSEY

J. S. WATERMAN & SONS SINCE 1832 FUNERAL SERVICE

LOCAL and DISTANT

GREATER BOSTON SINCE 1832

THE MEDICAL PROTECTIVE COMPANY

FORT WAYNE, INDIANA

the doctor's most secure source of security

PROFESSIONAL PROTECTION EXCLUSIVELY SINCE 1899

BOSTON Office:
Augustus F. Fox,
Representative,
11 Pemberton Square,
Tel. CApitol 7-0119

Founded 1879

RING SANATORIUM

EIGHT MILES FROM BOSTON

For the study, care and treatment of emotional, mental, personality and habit disorders.

On a foundation of dynamic psychotherapy all other recognized therapies are used as indicated.

Cottage accommodations meet varied individual needs. Limited facilities for the continued care of progressive disorders requiring psychiatric, medical, or neurological supervision.

Full resident and associate staff. Courtesy privileges to qualified physicians.

BENJAMIN SIMON, M.D.
Director

CHARLES E. WHITE, M.D.
Assistant Director

Arlington Heights
Massachusetts
ARlington 5-0081

Woodside Cottages

FRAMINGHAM, MASS.

A sanitarium specially adapted for nervous and convalescent patients who need rest and upbuilding in normal surroundings.
No committed mental cases.

ARTHUR H. WARD, M.D., *Medical Director*

GLENSIDE

JAMAICA PLAIN, BOSTON, MASS.

A small, attractively located sanitarium for nervous, mild mental or chronic illnesses.

6 Parley Vale Tel. JA 4-0044

BALDPATE, Inc.

GEORGETOWN, MASSACHUSETTS

Telephone GEO 2131

LOCATED IN THE HILLS OF ESSEX COUNTY
30 miles north of Boston

For the treatment of psychoneuroses, personality disorders, psychoses, alcoholism and drug addiction.

Psychotherapy is the basis of treatment; electric shock treatments, subcoma and deep coma insulin therapy when indicated; sleep treatment for withdrawal of narcotics.

Occupation under a trained therapist, diversions and outdoor activities.

G. M. SCHLOMER, M.D.
Medical Director

Wiswall Sanatorium

203 GROVE ST., WELLESLEY, MASS.

For the care of mild mental and nervous patients in country surroundings. Small grouping allows a homelike atmosphere and personal contact.

E. H. WISWALL, M.D., *Superintendent*
HALE POWERS, M.D., *Medical Director*
Tel. WE 5-0261

PROTEIN BOUND IODINE
TOTAL IODINE
FLAME PHOTOMETRY
Immediate Service
BOSTON MEDICAL LABORATORY
NORBERT BENOTTI — JOSEPH BENOTTI
Directors
19 BAY STATE ROAD, BOSTON 15, MASS.
KE 6-0348 and 0533

DAVID MEMORIAL NURSING HOME

BROOKLINE 46, MASS.
S. D. COHEN, R.N., *Supt.*
Convalescents — Invalid-Elderly
Accepted by Blue Cross - Blue Shield
Prolonged Illness Program
61 Park Street BE 2-3530

HANOVER HOUSE, INC.

West Hanover, Mass.

A sanatorium in the South Shore Area within easy distance from Boston.

Tel. Rockland 1690 — Quincy Office PR 3-6930

For the diagnosis and treatment of neurological diseases, emotional disturbances and personality disorders. All modern forms of specialized therapy (including electroshock) with emphasis on psychotherapy; treatment of alcoholism and related addictions on most modern, scientifically approved basis. Unusually attractive atmosphere, singularly free from "institutionalization."

Excellent nursing and medical care for limited number of chronic patients.

No committed patients.

Outpatient treatments for referred cases only.

ELSIE S. NEUSTADT, M.D., *Medical Director*
RUDOLPH NEUSTADT, M.D., *Clinical Director*

PERKINS SCHOOL

LANCASTER, MASS.

Devoted to the scientific understanding and education of children of retarded development. Five homelike and attractive buildings surrounded by 85 acres of campus and gardens.

FRANKLIN H. PERKINS, M.D.

Washingtonian Hospital

41 MORTON STREET, BOSTON 30, (Jamaica Plain) MASS.
Incorporated 1859

Conditioned Response, Psychotherapy, Antabuse, Adrenal Cortex and other drug therapies, Semi-Hospitalization for Rehabilitation of Male and Female Alcoholics.

Treatment of Acute Intoxication and Alcoholic Psychoses Included

State Outpatient Clinic and Social Service Department for Male and Female Patients

JOSEPH THIMANN, M.D., *Medical Director*
Consultants in Medicine, Surgery and the other Specialties
Telephone JA 4-1540

DELINQUENT ACCOUNTS
COLLECTED

Ethically — Courteously — Efficiently

Experienced Over 25 Years

Monthly Report Bonded

For particulars call or write

Medical Clearing Bureau, Inc.
110 Tremont Street, Boston, Mass.
HU 2-5570

PLEASE NOTE

Our stock of 1954 issues is badly depleted, making it most difficult to fill special orders for subscribers who are missing numbers and wish to bind their volumes complete.

If you have extra copies of the following and do not bind your volumes, won't you please send them to us.

January 7 and 14
February 4, 11 and 18
March 4, 11, 18 and 25
April 1, 8 and 22
July 1, 8, 15 and 22
September 2 and 9
October 7 and 14

We shall gladly pay 15 cents for each copy in condition suitable for binding and we shall reimburse you for postage.

Thank you,

Milton C. Paige, Jr.
Circulation Manager

ELECTRON PHOTOMICROGRAPH

Hemophilus influenzae 64,000 X

Hemophilus influenzae ("influenza bacillus") is a Gram-negative organism which grows only in the presence of hemoglobin. Contrary to its name, it is not the causative agent in influenza, but rather is commonly involved in

meningitis • chronic bronchitis • bronchiolitis
tracheobronchitis • supraglottic laryngitis • bronchopneumonia

It is another of the more than 30 organisms susceptible to

PANMYCIN* HCl

100 mg. and 250 mg. capsules
*125 mg./tsp. and 250 mg./tsp. oral suspension (**Panmycin** Readimixed)*

Upjohn

*TRADEMARK, REG. U.S. PAT. OFF.

4-ROOM DOCTOR'S OFFICE completely equipped. Air conditioned. Excellent location in West Medford. Address A172, *New. Eng. J. Med.* 3-eow-tf

USED instruments and equipment bought and sold. All types of repairs reasonably done. GALE SURGICAL SUPPLY CO., 6 Francis Street, Boston. (Opposite Peter Bent Brigham Hospital) AS 7-0777. B166-22-eow-tf

WANTED—Part-time office space, one or two days, weekly, in Concord or Lexington area, by obstetrician-gynecologist. Address A195, *New Eng. J. Med.* 10-4t

SUMMER COTTAGE—FOR RENT —Harwichport — 100 yards from beach. 5-minute walk to center. Cool and airy with good view. 3 bedrooms. Season or weekly. Address A204, *New Eng. J. Med.* 13-1t

CLINICAL BIOCHEMIST, Ph.D., director hospital laboratory, eight years. Blood grouping specialist, administration, publications. Address A206, *New Eng. J. Med.* 13-4t

FOR RENT — Office of late Dr. Thomas Forsley, Jr. of Billerica. Furnished and completely equipped for general practice. Centrally located. 30 River Street, Billerica Center. Telephone MOntrose 3-3407. B213-12-3t

AUDIOMETER for sale—ADC, model 50, in excellent condition—$195. Also Castle Electric Instrument Sterilizer — 16 inches long — $45. Address A203, *New Eng. J. Med.* 12-4t

PRIVATE TUTORING AVAILABLE nights and weekends in internal medicine or electrocardiographic interpretation. Address A205, *New Eng. J. Med.* 13-3t

LABORATORY TECHNICIAN desires position in doctor's office. Experience with E. K. G. and basal metabolism tests. MYstic 6-6037. B219-13-5t

MANUSCRIPTS, reports, medical records typed out neatly, accurately and distinctively with the added attraction of the free loan of my dictating machine or my tape recorder for that first draft. (After 6 p.m. and weekends)—GArrison 7-7758. B221-13-1t

OFFICES—BACK BAY—2, 3, 5-room modern offices for medical purposes. Doctor, lawyer, and so forth. Janitor and elevator service. Reasonable rent. For further information, call FA 3-3480 or FA 3-3671. B215-12-tf

WANTED—Three general practitioners to locate in growing industrial community. New well-equipped hospital. Located in heart of recreational area, Maine. Address A197, *New Eng. J. Med.* 10-4t

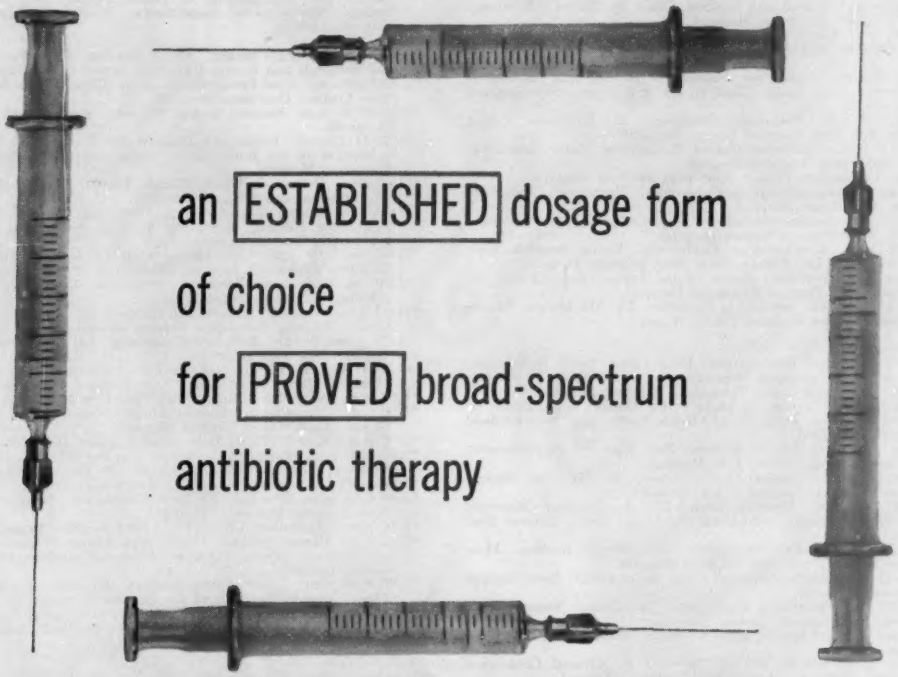
WANTED — M.D. for A-1 industrial plant, Boston area. Research and internal medicine—to age 50. Armed forces veteran preferred. No fee. Salary $10,000. Send resume to Queens Employment (Agency), 29-28 41st Avenue, Long Island City 1, New York. B220-13-1t

FOR RENT—Professional suite—College Avenue, Somerville, Mass. Newly decorated. Large reception room to be shared with dentist. Adequate parking. Professional location. Ideal for general practice or specialty. Call Dr. Segal, SOmerset 6-1900 or MOnument 6-4505. B222-13-1t

(Advertisements continued on page xvi)

Index to Advertisers

	PAGE
Ames Company, Inc.	iv
Baldpate, Inc.	xviii
Bilhuber-Knoll Corp.	xvii
Boston Medical Laboratory	xviii
Lester L. Burdick, Inc.	xiv
Ciba Pharmaceutical Products, Inc.	viii, Back Cover
David Memorial Nursing Home	xviii
Electroencephalographic Laboratory, Inc.	xvi
Federated Accounting Services, Inc.	xvi
Glenside, Inc.	xviii
Hanover House, Inc.	xviii
Hoffmann-LaRoche, Inc.	After xiv
Thos. Leeming & Co., Inc.	xxii
Eli Lilly and Company	x
Medical Clearing Bureau, Inc.	xviii
The Medical Protective Company	xvii
Parke, Davis and Company	ii, iii
Perkins School	xviii
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	xxi
Ring Sanatorium	xviii
W. B. Saunders Company	Front Cover
Julius Schmid, Inc.	vi
G. D. Searle and Company	xi
Sharp & Dohme (Division of Merck & Co., Inc.)	v
Smith, Kline & French Laboratories	ix
E. R. Squibb & Sons (Division of Mathieson Chemical Corporation)	xii
Storrow House (Massachusetts General Hospital)	xvi
Tweeds, Inc.	xv
The Upjohn Co.	vii, xix, xxiii
Warner-Chilcott	xiii
Washingtonian Hospital	xviii
J. S. Waterman & Sons	xvii
Wiswall Sanatorium	xviii
Woodside Cottages, Inc.	xviii
Worcester Medical Laboratory	xvi



an ESTABLISHED dosage form
of choice
for PROVED broad-spectrum
antibiotic therapy

TERRAMYCIN®
Brand of oxytetracycline
INTRAMUSCULAR

the *first* broad-spectrum antibiotic
available in this convenient parenteral form
for the treatment of a wide range
of infections due to susceptible organisms.

Supplied in single-dose vials. On reconstitution,
each single dose contains: Crystalline
Terramycin hydrochloride—100 mg.
Magnesium chloride—5%
Procaine hydrochloride—2%

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N. Y.*
Division, Chas. Pfizer & Co., Inc.

(Concluded from page 554)

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Rectal Administration of Anesthetics. Dr. Burnap. Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, APRIL 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. New England Deaconess Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital. House Officers' Association. The Causes and Management of Hyponatremia. Dr. Maurice B. Strauss. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, APRIL 13
New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m. Boston State Hospital. Psychiatry Seminar. Progress in Psychiatric Nursing. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:15 p.m. Chelsea Soldiers' Home. Management of Cardiac Disease. Dr. Samuel Levine. Quigley Memorial Auditorium, Soldiers' Home, Chelsea.
*7:30–9:30 p.m. Lahey Clinic Lecture. Diseases of the Pituitary Gland. Present Concepts of the Growth Hormone. Dr. Lewis M. Hurxthal. Physiology and Disturbances of Ovarian Function. Dr. A. S. Parker. Joslin Auditorium, New England Deaconess Hospital.

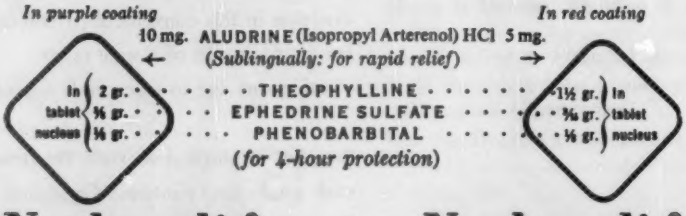
*Open to the medical profession.

In asthma... there's an excellent chance

your patient will prefer fast-acting, long-lasting

NEPHENALIN to other oral medications and to the nebulizer.

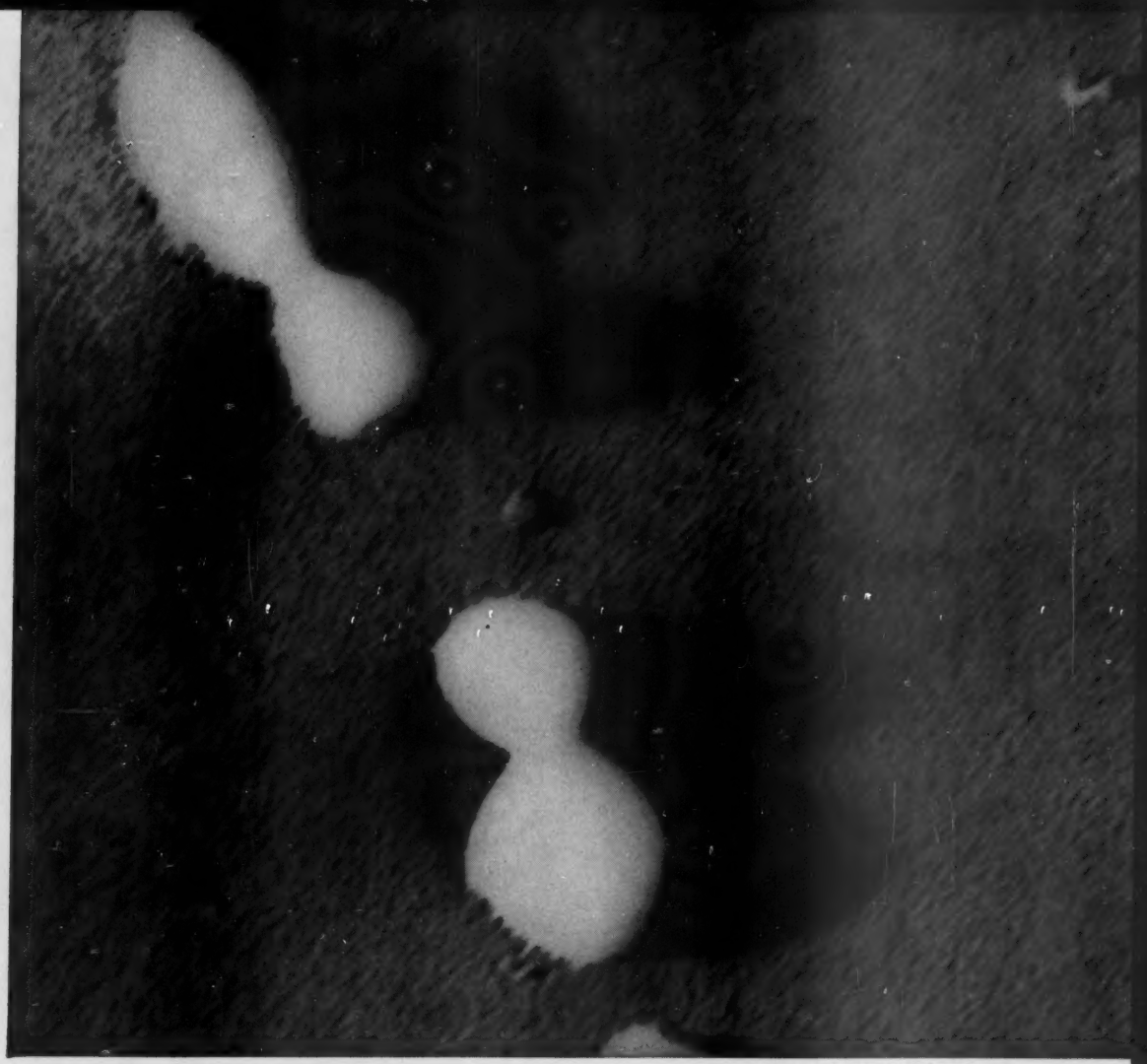
Two treatments in one tablet: first, hold under the tongue for five minutes; then swallow. This provides rapid bronchodilation from sublingual aludrine, then 4-hour follow-through protection from theophylline-ephedrine-phenobarbital. *Dosage:* One tablet as necessary (up to 5 tablets a day). In bottles of 20 and 100.



Nephenalin® (PURPLE) *for adults*

Nephenalin® PEDIATRIC (RED)

Thos. Leeming & Co. Inc. 155 East 44th Street, New York 17, N.Y.



ELECTRON PHOTOMICROGRAPH

Streptococcus pyogenes 36,000 X

Streptococcus pyogenes is a Gram-positive organism commonly involved in a great variety of pathologic conditions, including

scarlet fever • tonsillitis • pharyngitis • otitis media • sinusitis
bronchopulmonary disease • pyoderma • empyema • septicemia • meningitis
mastoiditis • vaginitis • rheumatic fever • acute glomerulonephritis

It is another of the more than 30 organisms susceptible to

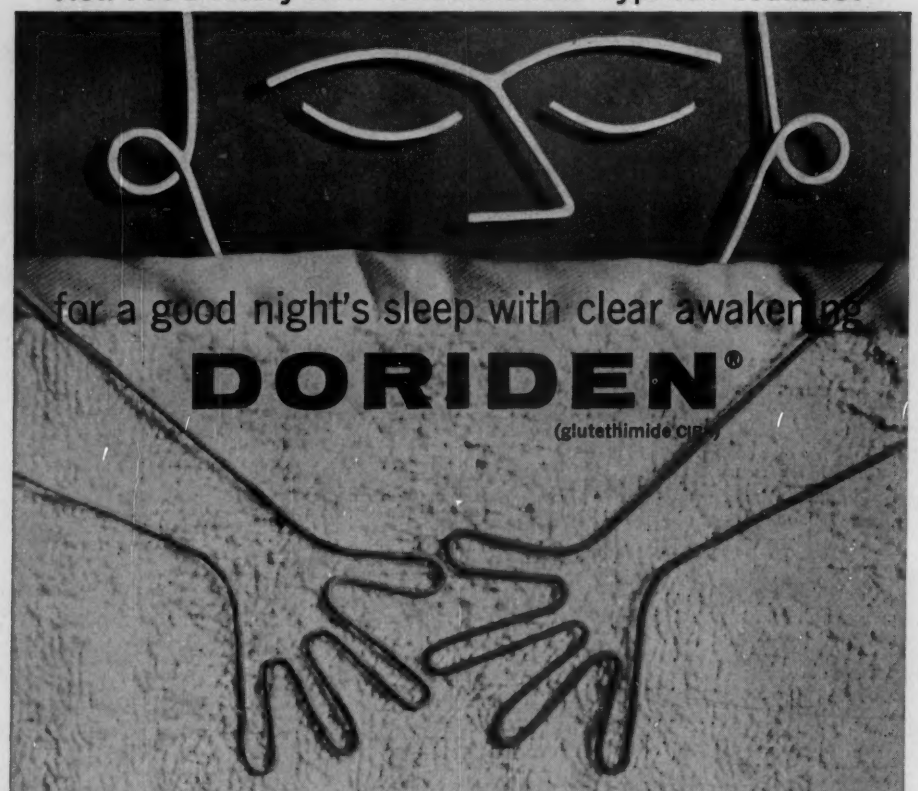
PANMYCIN* HCl

100 mg. and 250 mg. capsules
*125 mg./tsp. and 250 mg./tsp. oral suspension (**Panmycin** Readimixed)*

Upjohn

*TRADEMARK, REG. U. S. PAT. OFF.

Now . . . a totally new nonbarbiturate hypnotic-sedative!



for a good night's sleep with clear awakening

DORIDEN®

(glutethimide CIBA)

In most cases—

Rapid onset—15-20 minutes
Lasts 4-8 hours
No hangover

Dosage: 0.25 to 0.5 Gm. before bedtime.

Scored 0.25- and 0.5-Gm. tablets.

C I B A Summit, N. J.

2/2075M